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CONTENTS

THE FRANK E. BUNTS INSTITUTE

announces

A Course In

Diseases of the Gastro-Intestinal Tract

on

MONDAY, TUESDAY, and WEDNESDAY
APRIL 5, 6, and 7, 1937

A complete outline of the course and application blank will be found on pages 156 and 157

NEWER DEVELOPMENTS IN CHOLECYSTOGRAPHY

E. N. Collins, M.D., and Joseph C. Root, M.D.

Since the introduction of cholecystography by Graham and his coworkers in 1924[1,2], its importance in the diagnosis of dysfunction or disease of the gallbladder has become well established, but the technique of this procedure has not yet become standardized. After countless discussions relative to the merits of the intravenous versus the oral method of administering the dye, the oral method has been adopted generally. The newer developments have been regarded with keen interest and the clinician as well as the roentgenologist, in judging the reliability of a cholecystographic examination, now insists on knowing the details of the method used. In attempting to standardize the procedure we believe the following features should be considered:

1. The administration of multiple doses of the dye produces greater density in the visualized gallbladder than does the single dose, and it makes non-visualization of greater significance, without harming the patient.

2. The administration of large amounts of sugar and other carbohydrates preceding and during the examination facilitates the excretion of the dye by the liver, thereby adding greater significance to the cholecystographic findings.

3. One ounce or less of a mixture of egg yolk, lecithin, and glycerine, as recommended by Levyn[3], has been found to be as efficacious as the fat meal in emptying the gallbladder, and it has not interfered with the roentgen examination of the stomach and small intestine on the same day that the cholecystograms are made. Figure 1 shows a small opaque calculus in the gallbladder area, which, at this time, cannot be excluded as an opaque calculus. This patient was given 4 drams of the lecithin mixture and the second film was made one-half hour later. Figure 2 shows the gallbladder in a contracted state with the suspicious shadow outside the gallbladder area.

4. The use of pitressin[4] in the elimination of confusing shadows in that part of the intestinal tract which may lie over the area of the gallbladder has precluded the necessity for reëxaminations in such instances. It has also made possible the use of the multiple dose oral method of cholecystography on the same days that the barium meal examinations of the stomach and small intestine, or the barium enema examinations of the colon are made.

Sandström[5,6] introduced the "multiple" or "fractionated" method of cholecystography. He stated that "phenolphthalein preparations once

introduced into the system circulate for a rather long time in an enterohepatic cycle. After being eliminated through the liver and its intermediary, the bile, they are reabsorbed through the intestines and so on. By introducing orally during each phase of the cycle additional small

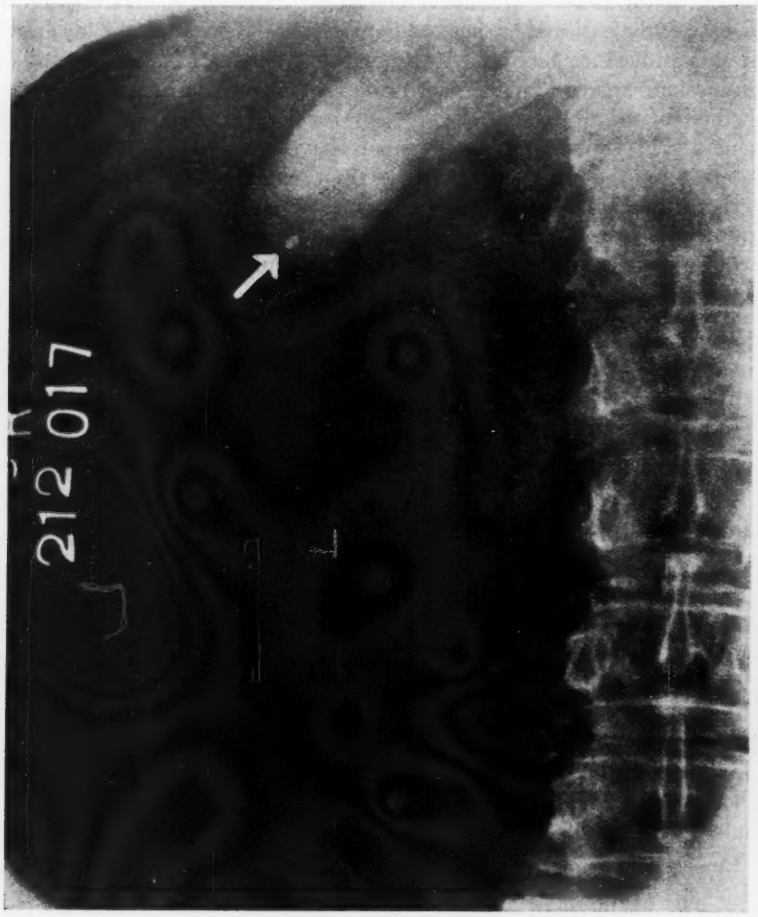

FIGURE 1: Questionable opaque calculus in the gallbladder region.

doses of the salt one may obtain a more complete absorption." In making a gastro-intestinal series examination following cholecystography, roentgenologists had frequently noticed the re-visualization of the gallbladder 30 or 40 hours after the administration of the dye and were ready to accept this statement. Sandström administered orally 7 to 10 grams of sodium tetraiodophenolphthalein in two or three divided

doses, allowing 2 or 3 days for the cholecystographic examination, and he found that greater absorption, resulting in greater density of the visualized gallbladder, was obtained without harm to the patient.

In 68 cases, Blomström and Sandström[7] supplemented cholecystography with the bromsulphalein test as a means of determining liver

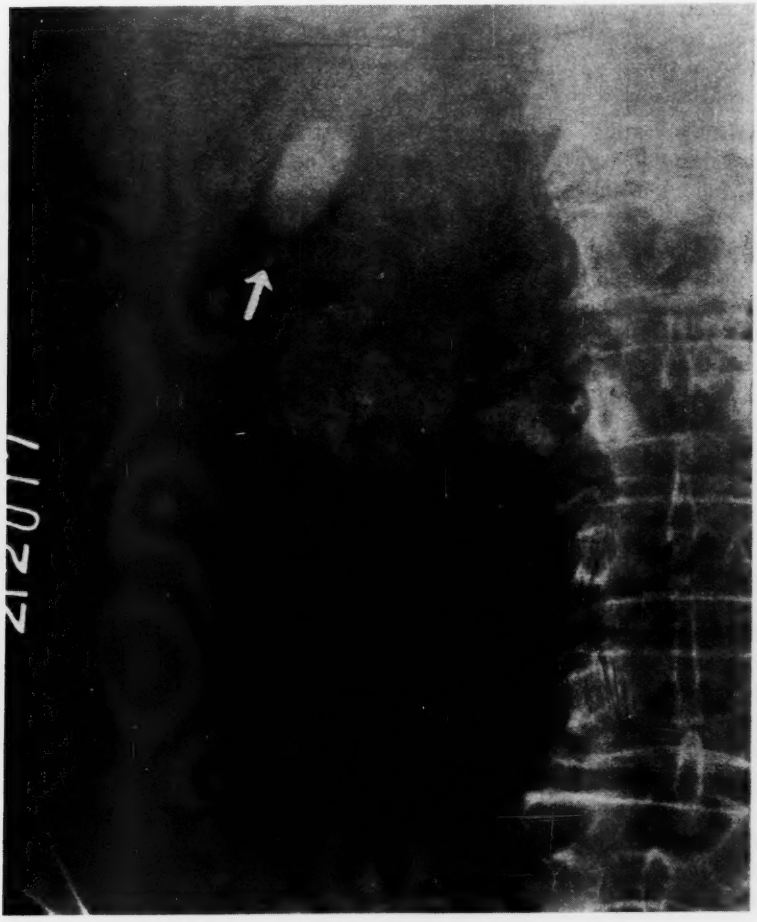

FIGURE 2: The gallbladder contracted after administration of lecithin mixture, throwing opaque shadow out of this region.

function in the event of non-visualization of the gallbladder by cholecystography. A high retention of bromsulphalein, over 40 per cent, excluded the possibility of visualization of the gallbladder because of liver damage, while a low retention, below 25 per cent, indicated that obstruction was located outside the liver parenchyma.

Sandström apparently allowed the patient to eat a mixed diet between the divided doses of the dye and so made no attempt to prevent emptying the gallbladder. Since carbohydrates had been shown to have no effect on the emptying time of the gallbladder in man[8], Whitaker and Ellsworth[9] modified the Sandström method by giving only carbohydrates between the two doses used in their "double oral" method. Whitaker[10] has since advocated that another carbohydrate meal be followed by a "third" dose of the dye if the roentgenograms at the end of 20 hours show no visualization of the gallbladder.

In his "rapid" cholecystography, Antonucci[11] demonstrated the value of using glucose with the intravenous method. Ten minutes after the intravenous injection of 125 cc. of a 40 per cent solution of glucose, the dye was injected. This, in turn, was followed by the subcutaneous injection of 24 units of insulin. Visualization of the gallblader was usually obtained within half an hour following the injection of the dye, and the maximum intensity was reached in 2 hours. It was Antonucci's opinion that glucose played an important part in the utilization of the dye and that the absorption of the dye in the liver necessitated the presence of glucose either in the blood stream or as converted from glycogen in the tissues, if the former became exhausted.

Graham, in 1933[12], demonstrated the value of combining intravenous cholecystography with determination of liver function, by use of the dye "iso-iodeikon" (sodium phenoltetraiodophenolphthalein). He found that a knowledge of the amount of this dye which was excreted by the liver was important in estimating the risk of performing operations on the biliary tract. In addition, it was of assistance in the interpretation of cholecystograms. By delaying operations until the proper medical treatment resulted in a reduction of high dye retentions to normal, the accuracy of the interpretation of cholecystographic findings was increased and the mortality rate for operations on the biliary tract was materially reduced.

Stewart and Illick[13,14] in their "intensified" oral cholecystography combined the fractionated method of administration of the dye with the administration of large amounts of sugar to facilitate the excretion of the dye by the liver, allowing only carbohydrate foods until noon of the third day when a fat meal was given to empty the gallbladder.

The Use of Pitressin During Cholecystography

One of the handicaps to accurate interpretation of cholecystograms is the presence of confusing densities, such as gas shadows, in the intestinal tract. Repeated examinations may be necessary before an accurate diagnosis can be made. In our experience, the use of cathartics and enemas has proved not only inadequate but it has actually resulted in greater

difficulties than were present before their administration. We have found the use of pitressin, the pressor fraction of posterior pituitary extract, very effective in solving this problem, and its use is a simpler procedure, requires less time, is less troublesome to the patient, particularly if the patient is not in a hospital, and it has not been attended by unpleasant reactions. However, because of its stimulating effect on the musculature of the gastro-intestinal tract as well as its vasoconstrictor effects, it has not been used when there is danger of perforation or mechanical obstruction in the gastro-intestinal tract or where there is evidence of cardiovascular disease. We do not use pitressin in the presence of advanced hypertension, and since we have noted a drop in blood pressure in 50 per cent of our cases in which it has been used, it is not given to a patient whose systolic blood pressure is below 100 mm. of mercury.

In a series of 1250 cholecystographic examinations, the use of pitressin was considered advisable in 200 cases, or 15 per cent. Effective results, i. e., the elimination of confusing shadows in the intestinal tract, were obtained in 87.5 per cent of these cases. In 76 per cent there were one or more stools within 30 minutes. In a more recent series of cases, in which the new ampoule containing 20 pressor units has been used, effective results have been obtained in 90 per cent of the cases.

The technique is merely the intramuscular (deltoid) injection of one ampoule of pitressin when the cholecystograms show confusing shadows in the intestinal tract. One hour later, additional cholecystograms are made. There has been no interference with roentgen examination of the stomach, small intestine or colon on the same day that pitressin is used. It is now employed routinely whenever there are confusing shadows in the intestinal tract, provided the contraindications mentioned are not present.

Figure 3 illustrates a case in which the second dose of dye was given the night following the routine examination of the stomach. It will be noted here that the entire gallbladder area is obscured by barium in the colon and no information about the function could be obtained by this cholecystogram. This patient was given 1 cc. of pitressin and a second film was made 45 minutes later. The barium was evacuated from the colon and we are now able to see in figure 4 a normally functioning gallbladder.

Comment

The diagnosis of cholecystic disease is usually simple when the patient gives a history of repeated attacks of biliary colic, particularly if these are associated with jaundice. In such instances, objective roentgen evidence for confirmation is obtained by cholecystography. In inflammatory diseases of the gallbladder, the physical examination usually

offers no assistance unless the patient is examined during the acute or subacute phase of the process.

In the absence of a history of biliary colic, accurate diagnosis may not be possible without cholecystography as well as the roentgen examination

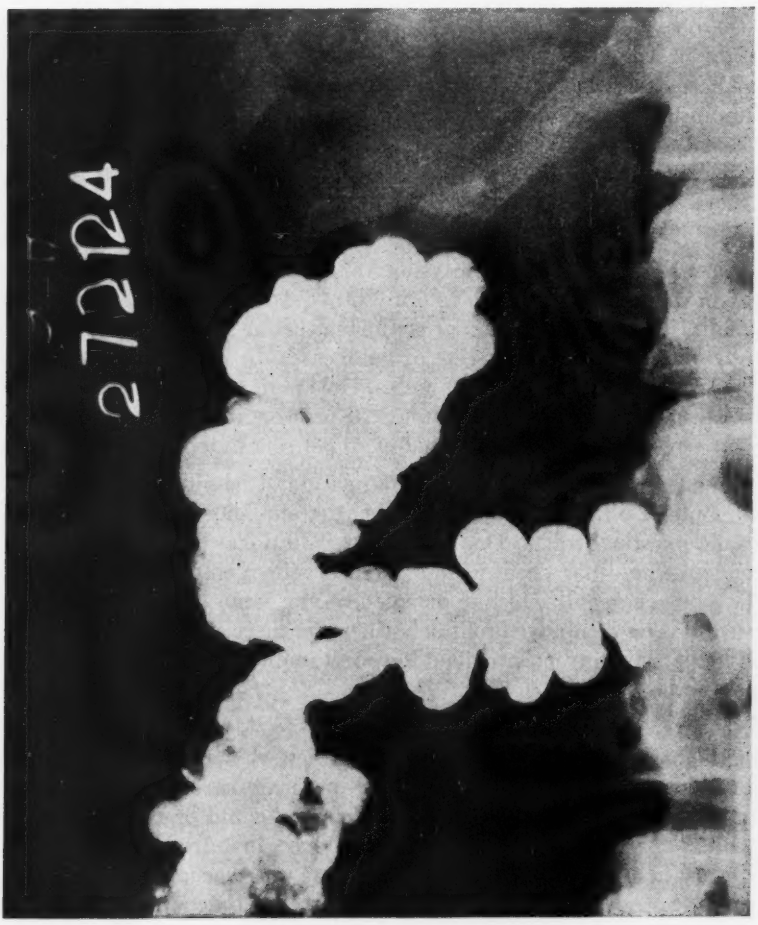

FIGURE 3: Gallbladder region obscured by barium in the colon.

of all organs which may cause symptoms simulating biliary disease. Nichols[15] has repeatedly emphasized the fact that since the sympathetic nervous system, through the superior and inferior mesenteric ganglia, receives fibers not only from the gallbladder, but also from the stomach, duodenum, right kidney, ureter, and colon, pain or distress in the right upper quadrant of the abdomen may be due to abnormality in any one or

several of these organs. The interpretation of so-called gallbladder dyspepsia or gaseous dyspepsia, as described in textbooks, when it is not associated with definite attacks of biliary colic, is open to question. Although patients who give a history of biliary colic, often have functional disturbances in the gastro-intestinal tract, Palmer[16] believes that, in the absence of this history, so-called gallbladder dyspepsia is in

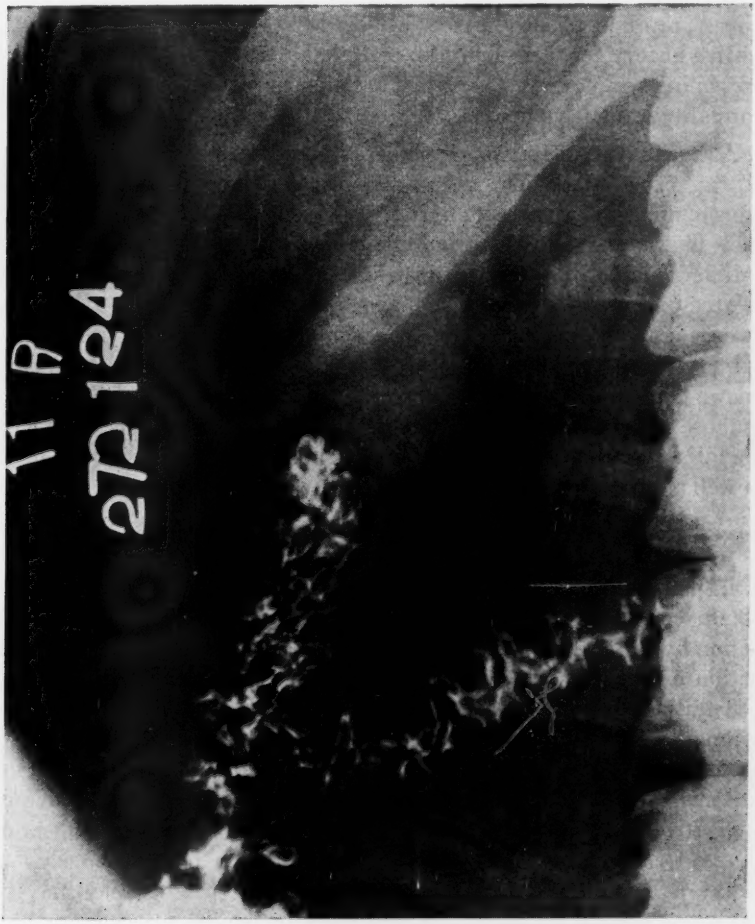

FIGURE 4: The normally functioning gallbladder visualized after administration of pitressin.

reality independent of the gallbladder and that it is not unlike the dyspepsia which occurs in patients who are not afflicted with cholecystic or other forms of organic disease. Our experience, also, leads to a similar conclusion. In instances where an indeterminate history is given, we

believe the roentgen examination of adjacent organs is equal to if not of greater importance than cholecystography alone.

The diagnosis of cholecystic disease can be made from the cholecystographic evidence alone, regardless of the symptoms, when it reveals the presence of gall stones, calcific deposits in the wall of the gallbladder, opaque bile in the gallbladder due to the presence of calcium carbonate bile[17,18], or of neoplasms[19] in the gallbladder. But, unless there is a suggestive history for these findings, care should be used in attributing the presenting symptoms of the patient to these causes without excluding abnormality in adjacent organs.

Although it is generally agreed that biliary disease is the most common *organic* cause of chronic gastro-intestinal symptoms in a middle-aged person, and since routine autopsies, both in this country and abroad[20,21], show that more than half the adults past 30 years of age had abnormal gallbladders and that approximately 20 per cent had gall stones, the relatively low incidence of previous clinical evidence of biliary disease in these cases makes one question the advisability of prescribing surgery on the basis of cholecystographic evidence alone[22]. It is well known that the best results from surgery of the gallbladder are obtained in those patients who have had definite biliary colic, and operations on the biliary tract are now seldom advised unless there is positive clinical as well as cholecystographic evidence.

Method

In patients who give a history highly suggestive of biliary colic, we obtain confirmatory evidence by making a cholecystographic examination by the oral method, and this is combined with a roentgen examination of the stomach and duodenum to exclude the possibility of a penetrating ulcer in the posterior wall of the duodenum which may cause symptoms suggestive of biliary disease. Plain films of the urinary tract are made at the time the preliminary plain films of the gallbladder region are made. If the roentgen findings in the urinary tract are positive or suggestive of abnormality, the patient is referred to the Department of Genito-Urinary Diseases for further examination before cholecystography is completed. Intravenous or retrograde pyelography may be indicated since there may be abnormality in the urinary tract as well as in the gallbladder, or the symptoms actually due to the former may be highly suggestive of the latter. When the plain roentgenograms of the urinary tract show no abnormality, the examination is limited to cholecystography and the roentgen examination of the stomach and duodenum, as mentioned.

In the much larger group of patients who give an indefinite history of digestive disturbances, motility studies of the intestine as well as barium enema examinations of the colon are added to the procedures mentioned above. The details of these examinations have been described[23,24]. This method was adopted by Nichols twelve years ago and the same procedures are used today.

In view of the fact that methods used in cholecystography are still not standardized, we believe the most practical method and the economic status of the patient, at least as it pertains to the time factor, are important considerations. Undoubtedly the fractionated or multiple dose method is the ideal procedure *per se*, but the single dose method, when combined with the roentgen examinations mentioned, has been found adequate in at least 90 per cent of our cases. When the cholecystographic findings result in non-visualization of the gallbladder or questionable findings, we administer a second dose of the dye the second night and this is combined with a continued high carbohydrate intake. If the cholecystograms the next morning show confusing shadows in the intestinal tract, pitressin is used. Barium studies of the stomach and small intestines are made in the meantime and as soon as the cholecystograms following the second dose of dye are satisfactory, a barium enema examination of the colon follows. In the time required to complete the fractionated method of cholecystography alone, we are able to make roentgen examinations of the urinary tract, using the single or double oral method of cholecystography, and at the same time to complete the roentgen examinations of the stomach, small intestine and colon.

Results

The evaluation of cholecystography is of course difficult, because relatively few of the patients in whom these examinations are made have abdominal operations. However, our operative findings during the past five years have coincided with the cholecystographic findings in either a positive or negative way in 95 per cent of the cases. In a series of 100 consecutive patients having abdominal operations, the cholecystographic findings were in error in 7 cases, an accuracy of 93 per cent from both the positive and negative standpoint. These examinations were made before the double dose oral method was used in cases presenting questionable findings, the single dose oral method having been employed in all these cases. The occasional use of a second dose of dye since that time is responsible for the accuracy of diagnosis mentioned previously. The

following table is a summary of the cholecystographic and pathologic findings in parallel groupings:

Cholecystographic Findings	*Number of Cases*	*Pathologic Findings*	*Number of Cases*
Normally functioning gallbladder without stones (negative)	4	Chronic cholecystitis (mild) without stones	3
		stone in cystic duct	1
Gall stones in a non-visualized gallbladder	21	Chronic cholecystitis with stones	21
Gall stones in a poorly visualized gallbladder	22	Chronic cholecystitis with stones	21
		without stones	1
Gall stones in a normally functioning gallbladder	22	Chronic cholecystitis with stones	21
		without stones	1
Non-visualization of gallbladder No opaque stones	27	Chronic cholecystitis with stones	21
		without stones	5
		grossly normal	1
Poorly visualized gallbladder without stones	4	Chronic cholecystitis (no stones)	4
Total	100	Total	100

In a consideration of the errors, there were four cases on the negative side in which normal cholecystographic findings had been obtained and little gross evidence of abnormality of the gallbladder was found at operation, but the microscopic diagnosis was chronic cholecystitis. In three of these, there were no stones. In the fourth case there was a stone in the cystic duct but none in the gallbladder. The clinical significance of a microscopic diagnosis of mild chronic cholecystitis in the absence of definite gross pathologic changes is disputed by many authorities.

On the positive side, a diagnosis of gall stones was made in two instances but operation did not confirm this; however, pathologic gallbladders were found. One of these two patients had a poorly visualized gallbladder which apparently indicated diminished function. The other positive diagnostic error was in a case of non-visualization of the gallbladder where the gallbladder at operation was grossly normal. This patient had a definitely pathologic appendix.

It will be noted that stones which were nonopaque to x-rays were present in 78 per cent of the cases in which the gallbladder was not visualized.

Evaluation of Cholecystographic Findings

Statistics relative to the value of cholecystography are usually based on operative findings. In most instances, positive clinical as well as

cholecystographic evidence of cholecystic disease exists before operation[24,25]. Kirklin and Blake[26] have recently summarized the cholecystographic evidence in patients who have not had abdominal operations but who have had a final clinical diagnosis of cholecystic disease and they find that the cholecystographic data coincide with the clinical diagnoses in approximately 90 per cent of the cases, a figure which is nearly equal to that found in patients having operations.

A normally visualized gallbladder may be pathologic. It would seem logical to believe that the routine use of the multiple dose method of administering the dye would increase this error which has been estimated to be 10 per cent[24,25] while the use of the smallest possible adequate dose should decrease this error. It should not be forgotten that pathologic gallbladders which are filled with stones commonly function with the cholecystographic dye. However, we are convinced that if the cholecystographic findings are normal, convincing clinical evidence is required to justify surgical interference.

Non-visualization of the gallbladder by cholecystogram without evidence of opaque calculi usually indicates a nonfunctioning gallbladder containing nonopaque (cholesterin type) stones with blocking of the cystic duct. But consideration must be given to the possibility of other causes of non-visualization, such as diseases of the liver or diseases in adjacent organs which may cause reflex disturbance in the dye-concentrating ability of the gallbladder or dysfunction in the sphincter of Oddi, at least at the time the examination is made. Non-visualization does not necessarily indicate a pathologic gallbladder, and such a diagnosis should not be made unless there is a suggestive history of biliary disease and all other causes for the symptoms have been excluded by a complete roentgen examination. It is in these instances that the multiple dose method of administering the dye, combined with a large intake of sugar, is definitely indicated. Added doses at each phase of the enterohepatic cycle usually are more effective than a re-check single dose examination at a later date, unless there is abnormality outside the biliary tract causing reflex disturbances which are relieved in the meantime.

Conclusions

1. Our operative findings during the past five years have coincided with the cholecystographic findings in either a positive or negative way in 95 per cent of the cases.

2. The multiple dose method of administering the dye is particularly indicated when the cholecystograms following the single dose method result in non-visualization of the gallbladder or when the findings are

indeterminate. However, in our experience the single dose method has been found adequate in at least 90 per cent of cases.

3. The use of pitressin has been found effective in the elimination of confusing shadows in the intestinal tract. Its use has precluded the necessity for re-examinations and has made possible the use of the multiple dose oral method of cholecystography at the same time that the roentgen examinations of the stomach, small intestine, and colon are made.

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ARTIFICIAL FEVER

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Hyperpyrexia by physical means is definitely established as a method for treating disease. At the present time physical agents may be utilized by various methods for this procedure. These are radiant heat, luminous heat cabinets, nonluminous heat cabinets, electric blankets, high frequency electrical currents, short wave diathermy, hydrotherapeutic methods, and hot water bottle and blanket method.

I do not wish to discuss the advantages or disadvantages of any of the above methods, but rather to review briefly the results that have been obtained by the use of these methods in the treatment of various pathological conditions.

Artificial fever is not new in the armamentarium of therapeutics, various substances having been used to produce fever in patients. Among the more common, the following may be mentioned: tuberculin, sterile milk, sodium nucleinate, typhoid vaccine, suspensions of sulphur in oil, relapsing fever, sodoku, and malaria. Inoculations with typhoid vaccine and malaria are very popular. However, after the original work of Neymann and Osborne[1] in 1929 in the production of artificial fever with high frequency currents, a new field of investigation was begun and has had a very rapid development.

In a review of the literature for 1935, Krusen[2] found that fever produced by physical means has been recommended for the treatment of no less than fifty different diseases. Results in the treatment of the majority of these diseases have not been encouraging, although for a selected group of patients this method has given promise of great usefulness. Neymann[3] has studied very thoroughly and given a comprehensive discussion of hyperpyrexia produced by physical agents. Sufficient clinical investigations have been completed in some of the following diseases so that it is safe to come to definite conclusions concerning the value of hyperpyrexia.

Gonococcic Infection: The most spectacular success has undoubtedly been obtained in the treatment of gonorrheal infections, including complications of prostatitis, salpingitis, periurethritis, cervicitis, and corneal ulcer. Desjardins and his coworkers[4] state that 90 per cent of their patients with gonorrhea, when given three to six sessions of sustained fever at 106 and 106.7°F. for five to eight hours were completely and permanently cured.

Before real effective therapy could be instituted, definite facts about the resistance of the gonococcus to heat had to be ascertained. Carpenter, Boak, Mucci and Warren[5] determined the vitro thermal death time of 130 strains of Neisseria gonorrhoeae and found this to vary between 6

and 27 hours at 106.7°F. These findings were employed in the treatment of 11 patients with specific gonococcic infection. Each patient was subjected to a single treatment of fever at 106.7°F. which was equal in length to the thermal death time of his particular culture. There was an immediate subsidence of all clinical symptoms and a bacteriologic "cure." These same authors have treated 118 patients in addition to the 11 listed above, 64 females and 54 males, with varying periods of hyperpyrexia at 106.7°F. lasting from 5 to 17 hours. Cultures from 80 per cent of these patients became bacteriologically negative and remained so for intervals varying from one month to three years.

In the treatment of gonorrhea of the female pelvis, the use of fever therapy combined with either diathermy to the pelvis or the Elliott treatments may be more effective than fever therapy alone. By the combined method of fever therapy and pelvic heating, one or two less treatments are necessary than with fever therapy alone. This method was developed by Bierman and Horowitz[6] when they found it difficult to secure a cure in some of their female patients.

Gonorrheal Arthritis: In gonococcal arthritis, the results of fever therapy have been unusually good. Hench[7] stated that after treatment with artificial fever, 70 per cent of the patients who had gonorrheal arthritis were free from symptoms and also regained complete function. An additional 10 per cent were markedly relieved and the remaining 20 per cent were unimproved. Whenever the surfaces of the joint have been destroyed and the synovial membranes have become thickened, complete restoration of joint movement can scarcely be expected. Hench's work indicates that the earlier in the course of the arthritis the treatment is given, the greater is the opportunity for complete subsidence of the infection and for almost complete restoration of articular function.

Syphilis—Early, Primary, and Secondary: It would seem that artificial fever therapy combined with chemotherapy affords better results than can be obtained by the use of either alone. In a recent article by Neymann, Lawless, and Osborne[8] 14 patients with early syphilis were treated with hyperpyrexia. This was combined with neoarsphenamine and bismuth salicylate in seven instances. All the seven patients treated with hyperpyrexia alone had further clinical or serologic evidence of syphilis after treatment ceased. All seven patients given the combined therapy became serologically negative and showed no clinical signs of syphilis for periods ranging from five to eighteen months after treatment ceased. Simpson[9] secured similar results in the treatment of 26 patients, all of whom were observed for six months to two and one-half years. His findings suggest that the logical time to institute combined fever-chemotherapy is immediately following the establishment of the diagnosis of syphilis.

Dementia Paralytica: Artificial fever has been used in the treatment of a total of 809 patients with general paresis as reported in the literature[3]. Of this number 226, or about 28 per cent, have had a complete remission, while 279, or 35 per cent, are reported as improved and are now for the most part said to be no longer in need of hospitalization. Twenty have died as a direct result of treatment. This is approximately 2.5 per cent.

Other methods of treatment of this condition bring about a rate of remission and good clinical improvement in approximately 30 per cent of the cases. During and just following the course of treatments with malaria, the death rate ranges between 10 and 30 per cent.

Tabes Dorsalis: It is necessary for more time to pass before it can be said that the progress of this disease has been arrested. Tabes, however, presents one dominant set of symptoms by which the arrest or progress of the disease can be judged—tabetic crises and lancinating pains. Hyperpyrexia has given permanent relief of these two symptoms. Ninety cases are reported in the literature[3] and 60 per cent of these patients have shown clinical improvement for the most part in the cessation of crises and pains.

Cerebrospinal Syphilis: The endarteritic, gummatous, and meningitic forms of tertiary syphilis usually respond to antisyphilitic therapy. However, this form is occasionally resistant to ordinary treatment. Hyperpyrexia extends definite hope to patients suffering from tertiary syphilis of the central nervous system who have not been helped by the older and more conservative forms of antisyphilitic therapy[3,9,10].

Syphilitic Optic Atrophy: Neymann[3], Beerman, Hirschfeld, Epstein and Paul[11] and others are of the opinion that no striking results have been obtained by the use of hyperpyrexia in this condition.

Culler[12], working with Simpson, reported the results secured in the treatment of 58 patients with various manifestations of ocular syphilis. He used the combined fever-chemotherapy technique of Simpson and his results show that some forms of ocular syphilis, particularly interstitial keratitis, syphilitic exudative uveitis, and choroiditis, respond well to this form of therapy.

Chorea: Artificial fever was first attempted in the treatment of this condition in 1929 when it was noted that a child improved after a fever developed following the administration of a sedative. Later, injections of typhoid vaccine for the purpose of elevating the temperature were used. This, however, frequently caused severe illness and occasionally death.

Hench[7] has collected approximately 30 cases in the literature in which artificial fever has been used. The results vary from improved

to "cured"; generally they are favorable. Three patients are reported as having had a recurrence.

Asthma: It has frequently been observed that fever associated with infectious diseases often temporarily and occasionally permanently controls the symptoms of allergic disease. It occurred to Feinberg[13] that the production of fever by artificial means might be of value in the treatment of chronic asthma and other allergic conditions.

In 1935, 117 patients were treated by this method[2]. The results were favorable in 104 cases, unfavorable in 10 cases, and slight and indifferent in at least three other cases.

Phillips[14] has used hyperpyrexia extensively in the treatment of bronchial asthma. He used it in more than 250 patients with an observation period ranging from 6 months to 3 years. Included in the group are patients of practically all ages—4 to 72 years—and both sexes are about equally represented. All types and durations of disease are included from the standpoint of chronicity, allergy, and pathology. In conclusion, he states that his results definitely indicate that fever therapy by physical means as a specific in the treatment of bronchial asthma will be disappointing and of no value except as a temporary measure, especially for breaking up an acute paroxysmal attack. On the other hand, when used in conjunction with other measures, it becomes one of the most valuable adjuncts in therapy.

Because of the severity of this treatment, fever therapy should not be attempted unless all other means have failed.

Chronic Arthritis: The clinical subdivisions of this disease are somewhat vague and ill defined; consequently there is a great deal of uncertainty and confusion about the classification. Most clinicians distinguish between two major types commonly designated as chronic, infectious, atrophic, proliferative or rheumatoid arthritis, and chronic senescent, hypertrophic, degenerative, or osteo-arthritis.

The latter group does not react well to this treatment; in fact, hyperpyrexia often makes the symptoms more severe.

The chronic infectious types respond best to hyperpyrexia if treatment is instituted early. Of this group, from 15 to 30 per cent of the patients are greatly benefited, another 30 per cent experience some relief, and between 40 and 55 per cent are not helped at all[3].

Other Diseases: Favorable reports appear in the literature on the treatment of the following diseases by artificially induced fever: multiple sclerosis, Parkinson's syndrome following lethargic encephalitis, undulant fever, malignancy, corneal ulcers, and iritis.

Contraindications to Artificial Fever: Contraindications to the use of fever therapy will vary according to the elevation of temperature

needed and also according to the general physical condition of the patient.

Every patient should have a thorough physical examination and clinical investigation. The following laboratory studies should be made: electrocardiogram, complete blood count, sedimentation time, and, if the patient is suffering from infectious and gonorrheal arthritis, he should have a thorough roentgen examination. Any other procedure necessary for complete and definite diagnosis should be made.

Advanced age is usually considered a contraindication for fever therapy. However, patients from two to seventy-five years of age are reported in the literature. Patients with advanced pulmonary tuberculosis, renal or cardiac disease should not be subjected to fever therapy. Any contraindication to major surgery is likely to be a contraindication to fever therapy.

Artificial fever should not be attempted as an office procedure. It should be done in a hospital or clinic where trained technicians are available and under the direction of a physician trained in this work.

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THE SIGNIFICANCE AND TREATMENT OF DELIRIUM OR CONFUSION FOLLOWING THYROIDECTOMY FOR HYPERTHYROIDISM

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The development of either mental confusion or active delirium in a patient on whom thyroidectomy has been performed for hyperthyroidism is an unfavorable prognostic sign. This reaction can be produced by a number of factors as is shown by an analysis of the causes of mental changes in the following thirteen cases of postoperative delirium or confusion. These thirteen cases occurred in a series of 200 consecutive operations on the thyroid gland for hyperthyroidism, an incidence of 6.5 per cent.

CAUSES OF POSTOPERATIVE DELIRIUM OR CONFUSION

Fifteen years ago, before iodine was used to prepare the patient for thyroidectomy and at a time when acute Grave's disease was much more common than it is today, the postoperative delirium of a typical thyroid crisis was a common occurrence. Today, however, a true thyroid crisis resulting in delirium is unusual. In this series of 200 consecutive thyroidectomies for hyperthyroidism, there were only two instances in which an active stimulated type of delirium was associated with marked elevation of temperature and pulse rate so that a diagnosis of thyroid crisis could be made.

In recent years we have seen relatively more elderly patients with nodular goiters and low-grade hyperthyroidism of long duration. It is in this type of case that we most commonly observe a state of postoperative confusion. Usually the patient is more than sixty years of age, is emaciated, feeble, and has had symptoms of hyperthyroidism for several years. Although cerebral arteriosclerosis is often a potent factor contributing to the mental symptoms, other factors also play a part in their development.

Confusion following thyroidectomy can usually be demonstrated to be the result of (a) liver failure, (b) kidney failure, (c) a cumulative effect of some drug or medication, or (d) an unclassifiable type of metabolic exhaustion. In order to demonstrate more clearly the factors causing the mental symptoms the cases will be presented in some detail.

MENTAL CONFUSION ASSOCIATED WITH LIVER FAILURE

In this series, a clinical syndrome which appears to be the result of hepatic failure has been responsible for the greatest number of cases of postoperative confusion and delirium in this series. Four of the thirteen cases of postoperative confusion could definitely be ascribed to

liver failure and a fifth in all probability was the result of the same process.

Lahey[1], Frazier[2], Coller[3], and others have emphasized the importance of the liver in the production of the severe postoperative thyroid reaction. Coller[3] has shown that the level of the serum bilirubin is definitely elevated and that dye tests show diminished liver function during the height of severe thyroid reactions.

Beaver and Pemberton[4] analyzed the autopsy findings in 107 cases of exophthalmic goiter and found that three types of hepatic lesions predominated: (1) Acute degenerative lesions, fatty metamorphosis, focal and central necrosis, and changes secondary to stasis of blood; (2) simple atrophy; (3) subacute toxic hepatitis and toxic cirrhosis. Clinically recognizable jaundice was present in 21.5 per cent of these cases. There appeared to be sufficient damage to cause disturbance of hepatic function which was detectable by clinical tests of hepatic efficiency in approximately 40 per cent of the cases. The acute lesions appeared to be in proportion to the severity of the disease. The atrophy was more marked in the aged. The subacute toxic atrophy and cirrhosis appeared more frequently among the older patients when the disease was severe and of long standing.

Weller[5] showed that the liver may be and frequently is involved in Grave's disease. He states that this has been demonstrated "*Clinically*, by the occasional occurrence of icterus . . . . . in this disease; *physiologically*, by the accumulating evidence of altered liver function in such patients; *experimentally*, by the evidence of hepatic dysfunction following administration of thyroid substance and thyroxin, and *morphologically*, by structural changes in the liver, varying from slight degrees of chronic hepatitis to a widespread degenerative necrotizing process which must be considered an 'acute yellow atrophy.' "

Youmans and Warfield[6] showed that hepatic function is impaired in certain instances of thyrotoxicosis. In 22 per cent of the cases they studied there was some loss of liver function. This impairment of liver function correlated roughly with the amount of weight lost, but not with the remaining clinical data.

This brief review of the literature indicates the importance of the liver in cases of severe hyperthyroidism, particularly in aged people.

Illustrative Cases

Metal Confusion Associated with Liver Failure

Case 1: The patient was a woman 61 years of age who had had a nodular goiter with severe hyperthyroidism for eight months. Auricular fibrillation

was present and there was slight evidence of cardiac decompensation. Twenty pounds in weight had been lost. The value for blood sugar while fasting was 88 mg. per hundred cubic centimeters. The basal metabolic rate was plus 71 per cent. The pulse rate at entry was 160 beats per minute. The value for hemoglobin was 61 per cent. After the administration of digitalis and iodine, the pulse curve showed an excellent response and all evidence of cardiac decompensation disappeared. The liver was not enlarged. The bases of the lungs were clear.

A left hemithyroidectomy was performed. Immediately after the operation a blood transfusion was given and the administration of a 10 per cent solution of glucose was started by the continuous intravenous drip method. Thirty-six hours after operation, the pulse rate rose to 140 beats per minute, but there was no evidence of cardiac decompensation and the general condition remained excellent. Forty-eight hours after operation, the temperature and pulse reactions were subsiding but the patient looked a little sallow. The icterus index at this time was 25 and the value for blood urea was 21 mg. per hundred cubic centimeters. She had become a little confused during the second day postoperatively and on the third day postoperatively she became delirious. In spite of the fact that the temperature and pulse reactions had subsided, the respiratory rate was elevated. The lungs were normal to auscultation and percussion and a roentgenogram of the chest showed no abnormality. On the fifth day the value for blood urea was 21 mg. per hundred cubic centimeters, the icterus index was 25, and the patient was still irrational. On the seventh day the value for blood urea was 27 mg. and for nonprotein nitrogen 30.8 mg. per hundred cubic centimeters. The icterus index had risen to 50. In spite of the fact that the temperature chart seemed to indicate that the patient's condition was improving she appeared, from a clinical standpoint, to be losing ground rapidly. On the seventh day she began to cough and raised blood-tinged sputum. The icterus index rose to 75 and on the eighth day after operation she expired.

Autopsy showed bronchial pneumonia and examination of the liver showed it to weigh 1760 grams and measure 22 x 18 x 8 cm. The capsule of the liver was thin and it was purple-brown-gray in color and mottled with areas of muddy yellow. Numerous phleboliths were scattered over the surface of the liver. Multiple sections of the liver revealed a yellow-gray substance which was rich in fat and had distinct markings. There was about the liver an appearance of slight biliary stasis. Small amounts of bile could be scraped from the surface. The consistency of the liver was comparatively firm. Sections for microscopic examination showed quite marked fatty degeneration. An examination of the urine for tyrosine and leucine crystals made shortly before the patient's death was negative.

Comment: In this case it will be noted that the thyroid reaction was not especially severe and that there was no evidence of cardiac decompensation after operation. The delirium became more pronounced on the second and third day when the thyroid reaction should be subsiding. At the same time the icterus index was rising steadily. A terminal pneumonia developed on the seventh day postoperatively and this complication was in all probability the indirect result of the hepatic insufficiency.

Case 2: The patient was a man 27 years of age who had had severe hyper-

thyroidism for one year. The pulse rate at entry was 120 beats per minute, the basal metabolic rate was plus 55 per cent, and 24 pounds of weight had been lost. There was no cardiac decompensation and no auricular fibrillation. The value for hemoglobin was 78 per cent. The value for blood sugar one hour P. c. was 180 and fasting it was 82 mg. per hundred cubic centimeters.

Thyroidectomy was performed, and the immediate postoperative reaction was not severe. On the second night, however, the temperature rose to 103°F. and the pulse rate to 170 beats per minute. (Fig. 1.) In spite of this, the patient's general condition remained excellent. There was no evidence of cardiac decompensation and the rhythm of the heart was regular. On the third day although the pulse rate had fallen to 120, the patient became drowsy and at times appeared slightly confused. The icterus index at this time was 30 and the value for blood urea was 36 mg. per hundred cubic centimeters. Glucose was administered intravenously and a diet high in carbohydrates was given. Complete recovery soon occurred. The icterus index again fell to normal.

Case 3: The patient, a woman 63 years of age, had had a nodular goiter with hyperthyroidism for three and one-half years. She had lost 34 pounds in weight. The pulse rate was 118 beats per minute at entry, the basal metabolic rate was plus 26 per cent, the value for hemoglobin was 84 per cent, and the value for blood sugar was 98 mg. per hundred cubic centimeters, four and one-half hours

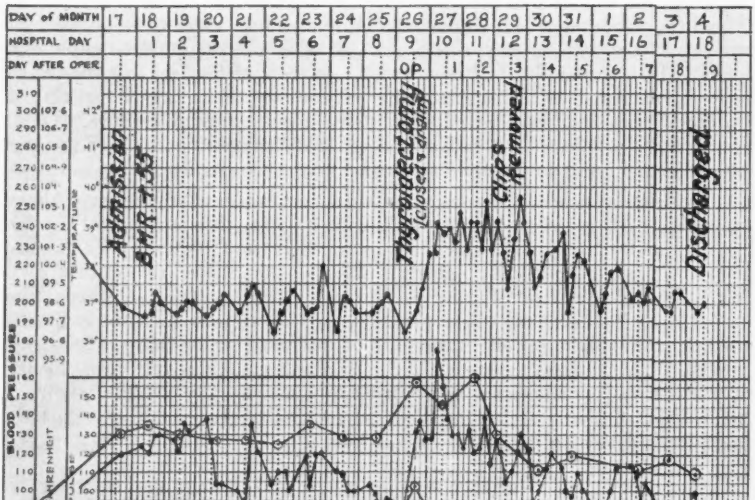

FIGURE 1: Temperature chart showing onset of confusion in relation to height of thyroid reaction.

P. c. Auricular fibrillation was present but there was no evidence of cardiac decompensation.

Thyroidectomy was performed and 36 hours after operation the pulse rose to 160 but by the third day it had fallen again to 95 beats per minute. At no time was there any evidence of cardiac decompensation. On the third and fourth days the patient was confused. The icterus index at this time was 15 and the value for urea was 30 mg. per hundred cubic centimeters of blood. The icterus index remained elevated until the sixth day postoperatively at which time it was still 15. After the administration of intravenous glucose and the forcing of high carbohydrate feedings, the mental symptoms cleared rapidly. At no time was the liver enlarged or tender.

Case 4: The patient was a woman 60 years of age who had had a nodular goiter with hyperthyroidism for two and one-half years. Auricular fibrillation was present but there was no evidence of cardiac decompensation. She had lost 25 pounds. The pulse rate at entry was 96 beats per minute, the basal metabolic rate was plus 32 per cent. The value for hemoglobin was 84 per cent and the fasting blood sugar level was 92 mg. per hundred cubic centimeters.

Hemithyroidectomy was performed on February 23, 1936, and the second lobe was removed one month later, March 24. The patient's condition was excellent for the first three days, but on the second day after the second operation she became somewhat confused. The icterus index on the third day postoperatively was 50 and the value for blood urea 45 mg. per hundred cubic centimeters. On the fourth day postoperatively the icterus index had fallen to 25. Glucose was administered intravenously, a high carbohydrate diet was given, and the mental symptoms cleared rapidly. During the height of the reaction there was slight epigastric distress and tenderness but the liver edge was not palpable.

Case 5: This patient showed no objective evidence of liver failure but it is probable that this was the fundamental cause of the reaction. She was 57 years of age and had had a nodular goiter with active hyperthyroidism for ten years. At entry the pulse rate was 120 beats per minute and the basal metabolic rate was plus 68 per cent. Twenty pounds of weight had been lost, the value for hemoglobin was 68 per cent, and the fasting blood sugar level was 107 mg. per hundred cubic centimeters. The patient was confused and delirious. She remained in the hospital for a month during which time she was given high carbohydrate feedings, Lugol's solution, and digitalis. The confusion gradually cleared.

Trial ligations of the superior thyroid arteries were performed and this procedure was followed by a minimal reaction. A subtotal thyroidectomy was then performed. Two days later, the blood urea was 24 mg. per hundred cubic centimeters and the icterus index was 5. Glucose in 10 per cent solution was started immediately after operation by the continuous intravenous drip method but was discontinued on the second day postoperatively. On the third day the patient became confused and remained so throughout the third and fourth days. The icterus index on the third day was 10 and the value for blood urea was 24 mg. per hundred cubic centimeters. The liver was not enlarged. Glucose was given intravenously, high carbohydrate feedings were forced after the fourth day postoperatively, and the patient's mental symptoms cleared rapidly. The appearance of the mental symptoms after the withdrawal of the glucose and their disappearance after resumption of glucose, coupled with the slight elevation

of the icterus index, suggest that liver failure was the cause of the symptoms (Table 1).

TABLE I

FOUR CASES OF LIVER FAILURE

Sex	F	F	F	M	Average
Age	61	60	63	27	53
Duration in months	8	30	36	12	21½
Weight loss in pounds	26	25	34	24	27¼
Hemogoblin per cent	61	84	84	78	77
Pulse rate	160	96	118	120	124
Basal metabolic rate	+71	+32	+26	+55	+46
Cardiac decompensation	+ at entry 0 postoper.	0	0	0	0
Confusion—day of onset	3rd	2nd	3rd	3rd (drowsy)	3rd
Jaundice—day of onset	5th	3rd	5th Not Clinical	3rd	4th
Icterus index (highest)	75	50	15	30	42
Blood urea (lowest)	21	45	30	36	33
Blood sugar	88 Fasting	92 Fasting	98 (4½ hrs. P.c.)	180 (1 hr. P.c.)	

COMMENT

In the first four cases of this group, in all of which there was objective evidence of liver failure, the average age of the patients was 53 years. The average duration of the hyperthyroidism was twenty-one and one-half months. The average loss of weight was twenty-seven and one-fourth pounds. The basal metabolic rates averaged plus 46 per cent. In no case was there any evidence of cardiac decompensation. The onset of the confusion or delirium occurred on the third day, usually at a time when the postoperative febrile reaction was subsiding. Jaundice was detected on the fourth day. The highest icterus indices averaged 42. The values for blood urea averaged 33 mg. per hundred cubic centimeters.

In several of the earlier cases it was observed that the value for blood urea was relatively low during the period when the icterus index was high and it was thought that this might be the result of failure of the liver to convert the amino acids to urea. At the same time it was appreciated that a relatively low value for urea could be expected as a result of the large quantities of fluid and carbohydrates which the patients were receiving. In order to determine which factor was responsible for the

low urea levels that had been observed, the blood amino acids were determined in a series of control cases and in two cases in which there was clinical evidence of hepatic failure. In neither of these cases was the amino acid level found to be higher than normal, an observation which Coller[3] has also made. In only one case of liver failure was a blood sugar estimation made before operation 1 hour P. c. but in this instance the value was 180 mg. per hundred cubic centimeters of blood. Patients with severe hyperthyroidism frequently have characteristic alterations of the glucose tolerance curves. In these curves, the blood sugar reaches its peak in the first and second hour, often rising to over 200 mg., but by the fourth hour it has usually returned to normal. This reaction may well be the result of the inability of the liver to convert glucose into glycogen, thus resulting in the appearance of sugar in the urine immediately after the glucose is given. The utilization of carbohydrate is, however, unimpaired and the curve falls rapidly to normal. Therefore, the glucose tolerance test may represent a sensitive test of the type of liver damage that is associated with hyperthyroidism.

Delirium Associated with a Thyroid Crisis

The thyroid storm usually reaches its maximum severity on the second night after operation. At this time the temperature and pulse rate are elevated, the patient is stimulated, restless, and in severe cases may be in such an active state of delirium that restraint is required. When the patient has had adequate preoperative preparation with iodine and bed rest, when glucose is administered intravenously by the continuous drip method, when morphia is given in doses sufficient to keep the patient at rest, and when the oxygen tent is used to control the hyperthermia, such a reaction is rare.

Case 6: The first patient in this group was a woman 50 years of age. Her basal metabolic rate was plus 55 per cent, the pulse rate was 140 beats per minute. She had an extremely active hyperthyroidism and a large diffuse goiter.

Forty-eight hours after a hemithyroidectomy, the pulse rate had risen to 160 and the temperature to 103°F. The patient appeared stimulated, was delirious, and had to be restrained. Adequate doses of morphia were given, she was placed in an oxygen tent, and glucose was administered intravenously. The temperature and pulse rate came down rapidly in response to this therapy and within twelve hours she was clear mentally.

Comment: This is the type of reaction which can usually be avoided if careful preoperative management is followed out and if immediately after operation the patient is given adequate sedation, glucose in 10 per cent solution by the continuous intravenous drip method, and oxygen therapy. In this case it would have been preferable to have avoided the reaction by instituting the above measures immediately

after the operation instead of waiting for indications of a thyroid crisis to occur.

Case 7: The patient was a woman 51 years of age who was suffering from severe recurrent hyperthyroidism. She also had diabetes mellitus. The pulse rate was 120 beats per minute and the basal metabolic rate was plus 71 per cent. The preoperative response of the pulse rate was satisfactory but, because of the severity of the hyperthyroidism, the age of the patient, and the presence of diabetes, it was decided to perform only a left lobectomy. The patient was a foreigner, did not understand English and was both frightened and uncoöperative. From the time she entered the hospital she insisted that she would die after the operation. Immediately after the operation a definite stridor developed in spite of the fact that only a left lobectomy had been performed and that the preoperative examination of the vocal cords showed both to be functioning normally. The blood calcium and phosphorus levels were within normal limits. A bilateral abductor paralysis of the vocal cords was found to be present. The explanation of this is not clear but the technical difficulties involved in removing the recurrent hyperplastic gland which was wrapped well around behind the trachea could conceivably result in injury of the nerve of the other side had it been displaced by the scar of the previous operation. The patient showed definite signs of anoxemia and at times was slightly cyanotic. She was kept in an oxygen tent, was given glucose intravenously by the continuous drip method, and large doses of morphia. The morphia, however, appeared to excite her and she became wildly delirious. On the second night after operation, the temperature rose to 103.6°F. and the pulse rate to 190. The evidences of anoxemia became more pronounced and an emergency tracheotomy became necessary. Following this procedure, she was quieted with 20 cc. of paraldehyde which was given by rectum. A blood transfusion was administered and the patient was kept in the Trendelenberg position to afford better drainage of mucus through the tracheotomy tube. The temperature and pulse rate rapidly responded to this treatment and the patient became rational again. Pneumonia, however, developed, and on the sixth day postoperatively she expired.

Comment: In this case the combination of poor morale, lack of coöperation, and anoxemia exaggerated by the patient's restlessness was sufficient to precipitate a thyroid crisis. The attendant delirium as well as the temperature and pulse reactions subsided rapidly after the correction of the anoxemia and the administration of adequate sedation, intravenous glucose, and oxygen therapy. It is important to remember in this connection that anoxemia secondary to insufficient respiratory exchange will precipitate a thyroid crisis with great rapidity but that a tracheotomy definitely increases the susceptibility to pneumonia. It is therefore a fine point of clinical judgment to determine whether tracheotomy, with its attendant liability to pneumonia, is justified in order to control the exacerbation of a thyroid crisis resulting from an insufficient respiratory exchange.

Delirium or Confusion Associated with Renal Insufficiency

Apathy, confusion, or delirium may be early signs of an impending renal insufficiency. In two cases in this series, in spite of the fact that

the fluid intake and urinary output were adequate and the specific gravity of the urine was relatively high, mental confusion was the first indication of an elevation of the blood urea.

Case 8: The patient was a man 81 years of age who had a nodular goiter with a definite low-grade hyperthyroidism. The pulse rate was 90 beats per minute and the basal metabolic rate was plus 11 per cent. He had lost 25 pounds in weight and all the classical signs of hyperthyroidism were present. Examination of the urine showed no abnormalities with the exception of a faint trace of albumin. A test of the urea clearance at entry showed normal kidney function, the urea level being 36 mg. per hundred cubic centimeters and the clearance 102 per cent in the first hour and 76 per cent in the second hour.

Following thyroidectomy, the temperature and pulse reactions were minimal, the temperature rising only to 100.4°F. and the pulse rate to 110 beats per minute. The output of urine varied from 1,050 to 1,980 cc. per day, averaging 1,500 cc. and the specific gravity varied from 1.020 to 1.022. On the fourth day postoperatively, the patient became confused and on the fifth day the value for blood urea was found to be 87 mg. per hundred cubic centimeters. Glucose was given intravenously, fluids were forced, the urea level gradually came down, and the mental symptoms cleared.

Comment: This case is interesting because it illustrates the point that uremia not infrequently develops following surgical operations in elderly patients, in spite of the fact that laboratory tests show their kidney function to be apparently normal. In this case the elevation of the blood urea occurred in spite of an adequate fluid intake and an output of over 1,500 cc. per day of urine of a normal specific gravity. We can do no more than speculate as to whether this type of reaction is the result of actual renal insufficiency or whether it is due to a relative insufficiency resulting from an increased breakdown of body proteins in these elderly patients after the trauma of operation. The fact remains that we have not infrequently seen such elevations of urea in elderly patients in whom preoperative tests have shown normal kidney function.

Case 9: The patient was a woman 75 years of age who had active hyperthyroidism with a pulse rate of 100 beats per minute and a basal metabolic rate of plus 36 per cent. The value for blood urea at entry was 51 mg. per hundred cubic centimeters and the urea clearance was definitely diminished—49 per cent in the first hour and 38 per cent in the second hour. On the second postoperative day the patient became confused and began to vomit. The urea rose to 75 mg. The daily output of urine averaged 2,000 cc. and the specific gravity was between 1.022 and 1.060. She improved strikingly with the administration of glucose intravenously and the mental symptoms rapidly cleared.

Mental Confusion Resulting from Sensitivity to Medication

It is often difficult to determine whether or not delirium and confusion are the result of an organic pathological process or are caused by intolerance to medication. In the following two cases the rapid improve-

ment of the mental symptoms after the withdrawal of drugs suggests that intolerance to these drugs may have been a factor.

Case 10: The patient was a woman 48 years of age who had had an adenomatous goiter with hyperthyroidism of long standing. She had been mentally clear until two days after entry in another hospital where heavy sedation, probably with barbiturates and bromides, was given. The patient became progressively more irrational and after about ten days in which she appeared to be constantly losing ground, she was transferred to the Cleveland Clinic Hospital. The pulse rate and temperature did not indicate that she was suffering from an acute hyperthyroidism and it was felt that the delirium must have some other cause. In view of the history of heavy sedation with barbiturates and bromides, these drugs were eliminated, and paraldehyde by rectum was used as a sedative. Ten per cent glucose in normal saline solution was administered intravenously, and the patient was placed on a high carbohydrate, high vitamin diet. On this regimen her condition improved rapidly, the delirium subsided within two days, and somewhat later thyroidectomy was performed successfully with a minimum postoperative reaction.

Comment: The rapid disappearance of the mental symptoms after the discontinuance of heavy sedation makes it highly probable that the delirium was the result of excessive sedation. Bromides, as a rule, are safe and effective sedatives for use in hyperthyroidism but cumulative effects may occur. The barbiturates must be used cautiously because they not infrequently produce marked confusion and occasionally even maniacal behavior in elderly patients with hyperthyroidism. When there is any tendency to mental confusion, morphine or paraldehyde usually affords safer and better sedation than the barbiturates.

Case 11: This patient was a woman 64 years of age whose pulse rate at entry was 120 beats per minute. The basal metabolic rate was plus 30 per cent. Auricular fibrillation was present. It had been impossible to determine definitely whether or not the patient had had digitalis before her entry and in view of the auricular fibrillation she was given the full dosage of digitalis. On the fifth day postoperatively when the immediate postoperative reaction had subsided, she began to vomit, became dehydrated, and was confused. The value for urea was 30 mg. per hundred cubic centimeters of blood, the icterus index was 5, and the leukocytes numbered 11,000. The digitalis was discontinued, an adequate fluid intake was restored, and within 24 hours the patient's mental symptoms had completely disappeared.

Comment: It is unusual for digitalis to produce mental symptoms but this does occur occasionally and it is possible that the digitalis together with the dehydration precipitated the state of confusion.

Miscellaneous

Under miscellaneous we must classify those cases in which the patients became confused following thyroidectomy, in spite of the fact that there was no objective evidence of liver failure, uremia, or drug intolerance. In these cases the reaction appears to be one of metabolic exhaustion

and is quite different from the stimulated delirium associated with a true thyroid crisis.

Case 12: The patient was a man 43 years of age who had severe hyperthyroidism with a pulse rate at entry of 120 beats per minute and a basal metabolic rate of plus 96 per cent. His response to bed rest and iodine was not satisfactory, the metabolic rate falling only to plus 68 and the pulse rate to 110. Ligations of the superior thyroid arteries were performed two days apart. No change in the pulse rate and no elevation of temperature followed these procedures, but the patient, whose weight had been constant on an intake of 5,000 calories, stopped eating and the caloric intake fell to between 1,000 and 2,000 daily. The fluid intake and output were normal. On the third day after the second ligation, although still practically afebrile, he became delirious; the pulse rate gradually rose to 140 beats per minute and his condition became critical. The intravenous administration of glucose was started by the continuous drip method, and morphia, in doses of one-half grain, was given to afford sedation. A nasal tube was inserted and 4,000 calories in the form of carbohydrates were given each day in 2,000 cc. of fluid. At the same time 5,000 cc. of 10 per cent glucose solution, (2,000 calories of carbohydrates) were given by the continuous intravenous drip method. Within two days the mental symptoms cleared and after the application of a radium pack to the thyroid he was sent home. The icterus index at the height of the reaction was 10 and the blood urea 39 mg. per hundred cubic centimeters.

Comment: In this type of case the excessive metabolism necessitates an enormous caloric intake. If this is diminished for any reason, the patient immediately uses up all reserves of liver glycogen and must of necessity oxidize his own tissues. It is impossible to state that this catabolic reaction is responsible for the mental symptoms but it is interesting to note how rapidly the symptoms clear up when an adequate caloric intake is reëstablished.

Case 13: The patient was a woman 66 years of age whose basal metabolic rate was plus 32 per cent. The pulse rate at entry was 104 beats per minute. During the preoperative stay in the hospital, an acute infection of the upper respiratory tract developed but this subsided completely before the operation was performed. On the second night postoperatively, the temperature rose to 102.2°F. The patient appeared exhausted and was almost pulseless. Auricular fibrillation was present. She was mentally confused and muttered constantly in an irrational manner. She was troubled with mucus but was too weak to raise it. She was placed in an oxygen tent, the foot of the bed was elevated, carbon dioxide inhalations were given, coramine was administered subcutaneously, and in a high Trendelenberg position she was able to raise the mucus. The cyanosis rapidly cleared. Three per cent glucose solution was given subcutaneously. The icterus index at this time was 5 and the value for the blood urea was 24 mg. per hundred cubic centimeters.

Comment: Although there was no definite evidence of liver failure in this case, it is quite possible that the reaction was secondary to hepatic insufficiency. The mental symptoms disappeared when the fluid and

carbohydrate intake was increased. We must, nevertheless, classify this as an undetermined type of metabolic exhaustion complicated by cerebral arteriosclerosis.

Summary

1. Thirteen cases of delirium or confusion occurring postoperatively in the course of 200 consecutive thyroidectomies for hyperthyroidism are reported and analyzed as to the causes of this reaction.

2. Liver failure was the most common cause, being responsible for four and possibly more of the cases in this series. Renal failure, drug poisoning, and thyroid crisis each accounted for two cases, and two cases were the result of an unclassifiable type of metabolic exhaustion.

3. Liver failure usually becomes apparent on the third day at about the time that the postoperative temperature and pulse reactions are subsiding. Mental confusion is usually the first sign and this is frequently accompanied by jaundice.

4. In order to avoid liver failure, it is essential to supply an adequate intake of carbohydrate. This can best be accomplished by administering glucose continuously by the intravenous drip method.

5. In elderly patients, even when renal function tests indicate no abnormality of the kidneys, there occasionally is a postoperative elevation of the blood urea to uremic levels.

6. The barbiturates or prolonged use of bromides may produce marked mental symptoms in patients with hyperthyroidism.

7. When a patient with severe hyperthyroidism fails to maintain a high caloric intake, the diminished glycogen reserve of the liver is rapidly depleted and the body proteins are oxidized. Once this cycle of catabolic processes is initiated, confusion or delirium may result, and unless the caloric intake is restored the outcome may be fatal. High carbohydrate, high calorie feedings given through a nasal tube are efficacious in restoring the nutritional balance.

8. Thyroid crisis is not as common a cause of postoperative delirium as it was in earlier years and can be more easily avoided than treated.

9. Two fatalities occurred in this series of 13 cases of mental confusion or delirium after operation for hyperthyroidism. Pneumonia was the immediate cause of death in both instances.

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THE TREATMENT OF CARCINOMA OF THE PROSTATE GLAND

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Treatment of carcinoma of the prostate gland is still the subject of considerable controversy among urologists, and the mortality from this condition remains high. In 1927, statistics from the United States Census Bureau showed that of every 100,000 deaths reported among men, 5.6 were caused by malignant disease of the prostate gland. In 1934, carcinoma of the prostate caused 5.2 of every 100,000 deaths, according to the Bureau of Vital Statistics.

During the past ten years, various methods of treatment have been employed at the Cleveland Clinic in an attempt to evaluate the merits of each. Early recognition of the malignant process is essential and an understanding of the most frequent site of primary involvement and the usual mode of extension are of paramount importance in determining the efficacy of proposed treatment.

While the majority of carcinomas involving the prostate gland probably arise in the posterior lobe[1], the initial lesion may originate in any portion of the gland or its accessory lobules. Geraghty[2] demonstrated that in the majority of cases the primary site of the lesion is in the posterior lobe, i.e., the portion of the prostate lying between the base of the bladder and the fascia of Denonvillier. This is in accordance with the observations of R. A. Moore[3] who studied fifty-two cases in which the lesion was sufficiently small that an accurate determination of the point of origin could be made. He found that 73.5 per cent arose in the posterior lobe, 8.8 per cent in the lateral lobes, and 14.8 per cent in the anterior lobe. Rolnick[4] states that the posterior lobe is the primary site of involvement in 80 per cent of the cases of carcinoma of the prostate but Randall[5] makes the statement that, "There is no evidence found in this series to substantiate a previous conception that is prevalent in the literature that malignancy of the prostate has its origin in the posterior lobe." In the series reported by Ferguson[6], 12 per cent of the carcinomas originated in or involved the lobules about the bladder neck.

That carcinoma of the prostate does not arise solely in the posterior lobe is evidenced by cases in which prostatectomy has been performed for apparently benign hypertrophy and pathological examination has revealed a small malignant lesion originating in lobes other than the posterior which is free from any malignant process. Rolnick[4] states that from 10 to 20 per cent of the operations performed at Cook County Hospital for benign prostatic hypertrophy have revealed carcinomatous involvement. Thus while carcinoma of the prostate arises in the pos-

terior lobe in the majority of cases, it must be appreciated that the primary lesion may originate in any portion of the gland. In doubtful cases, aspiration biopsy is of value in rendering a correct diagnosis, and there should be no hesitancy in employing this valuable procedure.

Extension of the Lesion and Metastases

Carcinoma of the prostate is said to be slow in growing and late in metastasizing. Bumpus[7] reported that metastases to the bones had occurred in 28 per cent of his cases when examination was first made, while Barney and Gilbert[8] found metastases in 58 per cent. In our series of 286 cases, radiological evidence of osseous metastases was present in ninety-five or 33 per cent, and in thirty-nine there was evidence of lymphatic extension.

Barringer[9] has stated that the carcinoma was confined to the capsule in only 2 per cent of his cases when the patient was first seen at the Cancer Memorial Hospital. Colston[10] found that thirty-six of 1,040 cases of carcinoma of the prostate were suitable for the radical operation.

According to Ewing[11] the clinical course of prostatic carcinoma is dependent on the structural type of the tumor, different forms appearing as radically different diseases. In studying the growth and extension of prostatic carcinoma, invasion of the perineural lymphatics is seen to occur early; however, metastases and extension beyond the capsule occur later. From his studies of the extension of this malignant lesion, Moore[3] believes that when the primary focus is in the posterior lobe, there is an early spread in the cephalocaudal direction just beneath the capsule. This extension, however, rarely crosses in the midline. If the lesion originates in the anterior lobe, the spread is in a more lateral direction and it crosses the midline. Moore states that a lesion arising in the lateral lobe is usually confined to one section which is less than 8 mm. in diameter, until it spreads laterally to the capsule, at which time it becomes similar to a lesion of the posterior lobe. In analyzing the cases at the Cleveland Clinic, early recognizable tumors of the prostate were rarely seen, and in most cases extension beyond the confines of the gland had occurred or metastases were demonstrable at the time of examination.

Treatment

In considering the treatment of carcinoma of the prostate, the procedure to be instituted varies with the conditions present and we believe four groups may be considered.

1. Cases in which minute lesions are associated with prostatic hypertrophy for which prostatectomy has been performed and carcinomatous involvement has been found on miscroscopic examination.

2. Cases in which the carcinoma is confined to the prostate, or in which only early involvement of the vesicles is present.

3. Cases in which the lesion is more extensive, not confined to the prostate, and not producing urinary obstruction.

4. Cases in which the lesion is not confined to the prostate and urinary obstruction is present.

As stated previously, it is estimated that microscopic evidence of malignancy is found in from 10 to 20 per cent of the cases in which prostatectomy is performed for benign hypertrophy, and in our hands the best results have been secured in this group of cases. Barringer[12] has stated that foci of the carcinoma are frequently present in the periprostatic tissue and that manipulation during operation is responsible for squeezing cancer cells out into the surrounding tissue. Following the surgical procedure in this group of cases, it has been our rule to use high voltage roentgenotherapy and to examine the patient frequently for any evidence of recurrence.

In a series of twenty-six prostatectomies for benign hypertrophy in which a malignant lesion was found by the pathologist, no radiation therapy was utilized in seventeen cases, and the average span of life was 35 months. Postoperative roentgenotherapy was employed in seven cases and radium was used in two with a resultant span of life of 48 months. In a second series of twelve cases in which the possibility of malignancy was considered at the time of operation, the seminal vesicles were removed also. Three patients in this series died following operation; seven received radiation treatment postoperatively, and the average duration of life was 12.6 months. Two patients did not receive roentgenotherapy, and the average span of life was 17.2 months.

The radical perineal operation is to be considered in cases in which the growth is confined to the gland or when there is early extension to the vesicles with no evidence of metastasis. This procedure was used in four cases in this series. In three, no radiation was recommended postoperatively and the average span of life was 17.3 months. In one instance, roentgenotherapy was utilized, and the patient lived for 16 months.

Young[13] reports a series of forty-two cases in which the radical operation was used. The operative mortality was 9.5 per cent and 52 per cent of the patients who survived the operation lived over five years. G. G. Smith[14] likewise reports that fifteen of twenty-six patients operated upon by this method lived without recurrence and apparently were cured. Therefore, when it appears technically possible to perform the radical operation, we believe such a procedure is acceptable and justifiable.

When the lesion has extended beyond the confines of the prostate and when extensive involvement and metastases are present without urinary obstruction, high voltage x-ray and radium assume priority in treatment, although a cure rarely or perhaps never can be secured by this method. A retardation of the growth of the tumor and alleviation of the patient's pain as well as cessation of hematuria may be noted.

In a series of 102 cases, radiation has been the only treatment instituted. Roentgenotherapy alone was used in eighty-three, and the average span of life was 16.2 months. Radium alone was employed in nine with an average span of life of 11 months, while in ten cases in which both radiation and radium were used, the average duration of life was 13.9 months.

Finally, in the group of cases in which symptoms of urinary obstruction predominate, we believe transurethral resection followed by roentgenotherapy is advisable. Caulk and Boon-Itt[15] reported a series of eighty-one cases in which the punch operation was employed alone or in combination with radiation or radium. They found that the combined treatment yielded the best results; 10 per cent of their patients were living or had lived five years after operation.

We have performed sixty-two transurethral resections for carcinoma of the prostate. This was the only treatment thirty-two of the patients received and the average span of life was 24.7 months. In twenty-seven, postoperative roentgenotherapy was instituted, and the average span of life was 24.9 months. In two cases, combined radiation and radium therapy were employed, and the patients lived for an average of 30 months. One patient died followed operation.

In the vast majority of cases, the symptoms of obstruction can be relieved by transurethral surgery. Although postoperative roentgenotherapy did not noticeably increase the span of life in our series, relief from pain was experienced following its administration. The mortality rate with this procedure is extremely low, and in these sixty-two cases, only one death occurred. We believe transurethral resection is preferable to suprapubic cystotomy or the use of an indwelling catheter. In some instances, it may be necessary to repeat the procedure but, in the majority of cases, relief from symptoms of obstruction occurs following removal of a sufficient amount of tissue.

Conclusions

1. Early diagnosis is essential in the treatment of carcinoma of the prostate.

2. Aspiration biopsy may afford a means of recognizing the malignant lesion before it spreads beyond the confines of the capsule.

3. Radical surgery followed by roentgenotherapy is the procedure of choice in the small percentage of cases in which it is technically feasible.

4. Transurethral resection affords a means by which the obstruction may be eliminated and the mortality rate reduced to the minimum.

5. In inoperable cases, roentgenotherapy is of value in retarding the growth of the tumor, eradicating or lessening the pain, and reducing the bleeding.

6. Careful follow-up observation should be employed in order to note the presence or absence of recurrences.

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NASAL ALLERGY

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The incidence of nasal allergy has been reported by several workers. Hansel[1] found that of 1,000 patients seen in routine office practice, there were 324 with all types of nasal complaints, and among these, 142 had nasal manifestations of allergy. In other words, about one-third of the patients had primary nasal complaints and 44 per cent of these had nasal allergy. The incidence of allergy among all patients was 14.2 per cent. Baum[2], according to a recent report, found that among 2,000 similar patients, 700 or about one-third had primary nasal complaints, 191 of which were found to be due to nasal allergy. Baum found, therefore, that 27.3 per cent of the patients with nasal complaints had allergy, and that the incidence of allergy in an otolaryngologic practice is about 10 per cent.

In a review of the cases of 514 patients seen in the Department of Allergy at the Cleveland Clinic during a six months' period in 1933, 326 or 63 per cent had, as major complaints, pollinosis, bronchial asthma, allergic bronchitis, perennial nasal allergy, and nasal allergy and sinusitis. In a review of cases of allergy seen in 215 children in 1934 and 1935, upper respiratory and respiratory allergy were noted in 166 or 77 per cent. An analysis of 1,174 consecutive new patients in the Department of Allergy during 1935 was made in an effort to classify the presenting major problems. Of these patients, 640 or 55.4 per cent had major problems of respiratory allergy, which included seasonal and perennial nasal allergy, nasal allergy and sinusitis, bronchial allergy, both asthma and bronchitis, and 534 or 44.6 per cent had symptoms of cutaneous, ocular, cerebral or gastro-intestinal allergy. This large incidence of respiratory allergy is due to several factors, chief of which is the interest that has been created in the study of respiratory allergy in otolaryngology, and secondly to the climatic conditions prevailing in the region of the Great Lakes.

Normal Histology of the Mucous Membrane of the Nose and Paranasal Sinuses

The mucous membrane of the nose and paranasal sinuses is divided into parts controlling the respiratory and olfactory functions. Only a small portion of each nasal fossa is concerned with the functions of the olfactory sense.

The part controlling respiratory functions consists of normal epithelium of the stratified, ciliated, columnar type which is comprised of tall surface cells bearing cilia and irregular supporting columnar cells. The surface of the epithelium is interrupted by outlets of the glands. Varying numbers of goblet cells appear between the ciliated cells. The

epithelium undergoes changes according to the presence of infections, irritants, etc., and then cuboidal, stratified cuboidal, squamous or transitional types are found.

Beneath the normal epithelium is the basement membrane, which is thin and collagenous in character and probably originates from connective tissue. These cells stain poorly. This layer is perforated with fine openings to permit the passage of leukocytes and tissue fluids.

The tunica propria, or stroma, extends from the basement membrane to the bone. This is a network of blood vessels, lymphatics, nerves, glands, and certain cellular elements. It is divided into three parts: (1) the subepithelial, which consists of a fine capillary network, and lies between the basement membrane and the area of the glands; (2) the area of the glands; (3) the portion from the area of the glands to the periosteum and vascular zone which contains large blood vessels and cavernous sinuses. The vascular supply is deep, periosteal, glandular, and subepithelial capillary. Innervation of this blood vessel system is derived from two sources—the vasoconstrictors which are derived chiefly from the cervical sympathetic system, and the vasodilator fibers which come mostly from the vidian nerve.

Three types of glands are present—the mucous, serous, and mixed. These are lined with mucous and serous secreting cells, and by means of small ducts they open upon the free surface of the epithelium.

The cavernous spaces represent the venous plexus and assume the character of erectile tissue. They are especially well developed along the dependent border of the inferior turbinate and posterior extremity of the middle turbinate and along the adjacent portions of the nasal septum. Circular and midlongitudinal bundles of smooth muscle are embedded in the walls of the venous channels and are enmeshed in connective tissue stroma. These are controlled by nerve reflexes which influence the filling and emptying of these spaces.

The paranasal sinuses, which are lined with mucous membrane, are continuous with the nasal fossa and are characterized by thin membrane, few glands, and no characteristics of erectile tissue.

Histopathology of Allergy

The changes which characterize the histopathology of allergy are well exemplified in the specific changes caused by allergy in the nasal mucous membrane and paranasal sinuses. Therefore, a brief review of these changes will illustrate the characteristic histopathologic findings of nasal allergy. Kline and Young[3] of Cleveland have considered the changes in allergic tissues as reversible or irreversible. In the reversible type there is resorption of edema which leaves no permanent change in the tissues. In the irreversible type, chronic edema and

certain other changes in the tissues become permanent in nature. However, for practical purposes, further study must be made of allergic disease of the nasal passages, a review from the standpoint of allergy alone not being sufficient. This is necessitated because secondary or superimposed infections and other irritating factors as well as allergy influence the permanent changes.

The work of several investigators has shown that the reactions due to allergy are dependent upon the degree of sensitivity of the tissues and the shocking dose of the offending allergen. The tissue changes may, therefore, vary from simple edema with eosinophilic infiltration, which has a tendency to resorb, to permanent changes with chronic edema and eosinophilic infiltration plus inflammatory changes which are the result of degeneration and necrosis, as noted in the Arthus' phenomenon. It must be noted that certain inherent tendencies appear to be present in the tissues of individual patients as far as the degree of edema or capillary permeability is concerned. The degree of sensitivity of the tissues rather than the nature of the offending allergen must play the most important part in this process. Kline and Young[3] have emphasized that this inherent and individual sensitivity of tissues must also be a factor in the determination of the nature of the secondary changes which occur in the blood vessels and other structures of the mucous membrane. This explains in part the tendency for sudden and extreme reactions of edema to develop quickly in the tissues of certain individuals whereas, in other persons, prolonged exposure to the same allergens does not produce such marked changes.

It must also be borne in mind that the histologic nature of the paranasal sinuses is of such character as to influence the development of extensive edema and formation of polyps. The entire thickness of the mucous membrane may become involved in the edematous process so that the whole sinus cavity is occluded. This is particularly true of the anterior cells of the ethmoids and the tissues of the antrum. The tendency for edema to form near the ostia is noted and this is due to the looseness of the mucous membrane at this location.

Eosinophilic infiltration is the second characteristic reaction of tissues in the presence of allergy. Although considerable difference of opinion is expressed as to the formation of eosinophils, it is generally conceded that they form in the bone marrow and that blood eosinophilia is only an index of the number of cells in transit from the bone marrow to the tissues suffering from allergic shock. There is no constant relationship between the degree of blood eosinophilia and the symptoms of the patient. This can be said in part of tissue eosinophilia, there being no absolute index after the allergic reaction is firmly established.

It is to be noted that the cellular changes of a secondary character, such as the presence of lymphocytes, plasma cells, and monocytes, are likewise noted in small amounts in the tissue reactions in allergy. There is a noticeable absence of the fibrous connective tissue proliferation that is so frequently seen in infections. In the acute cases, resorption of the edema takes place with a return to normal cytology, while in the chronic recurring forms, the edematous processes tend to become permanent because of injury to the blood and lymphatic systems. Likewise, superimposed acute and chronic infection promotes infiltration with inflammatory changes and eventual fibrosis of blood vessels and supporting tissues with predisposition to permanent changes.

Chronic edema and fibrosis produce closure of the ducts of the glands with resultant cystic formations.

Hansel[1] showed in the following table (Table 1) the changes in different tissues due to allergy, infection, and allergy and infection.

Cytology of Nasal and Paranasal Sinuses in Allergy

The shock tissues or tissues of reaction in allergy are characterized by edema and eosinophilic infiltration. The demonstration of eosinophils in secretion is utilized as a means of corroborating the diagnosis of nasal allergy. The investigation of many workers on the importance of determining the number of eosinophils in secretions from the nasal and paranasal sinuses has emphasized the value of a study of the cytology of these secretions as an aid in the diagnosis of allergy. The recognition of allergy as a factor in diseases of the nasal passages and sinuses has necessitated a reclassification of conditions which were once considered to be inflammatory, particularly the non-suppurative and polypoid forms of disease. These may be classed pathologically in the following manner:

1. Of infectious or suppurative origin
2. Of allergic origin
3. Of allergic origin with superimposed infection.

With a very careful history and clinical examination, a diagnosis can be made in a large percentage of patients. Often, it is not feasible or possible to take a biopsy of tissues, but the cytology of the secretions may be considered as an accurate index of the pathology occurring in the tissues. The physician should be capable of determining the presence or absence of allergic manifestations, and whether infection complicates the allergic state through the clinical history, the state of the nasal tissues upon examination, the roentgen examination of the sinuses, the bacteriology, the cytology of secretions, and the histopathology of nasal and paranasal sinus tissues.

In considering the cytology of the nasal secretions, it is often necessary to make repeated examinations, particularly if the clinical history

TABLE 1

	Allergy	*Infection*	*Allergy and Infection*
		GROSS CHANGES	
	Mucous membranes—pale, sometimes normal or red. Edematous thickening. Polyps. Tissue, soft. Secretion, watery or mucoid.	Mucous membranes—red. Firm, thick, swelling Polyps, rare. Tissues, firm, fibrous, granular. Secretion, purulent.	Mucous membranes—pale or pale red. Edematous thickening Polyps. Tissues more fibrous and firm. Secretions, clear and purulent.
		MICROSCOPIC CHANGES	
Epithelium	Varying types. Normal to marked hyperplasia. Edema. Swelling.	Varying types of hyperplasia, often marked thickening assuming squamous characteristics. Surface irregular and granular.	From simple swelling or thickening to marked squamous proliferation. May be granular in areas.
Basement Mucous Membrane	May be absent. Slightly thickened. Markedly thickened. (Asthma)	May be markedly thickened to wide layer. Increased fibrosis. Hyaline appearance.	Usually thickened in various degrees.
Subepithelial Layer Fibrous tissue	Edema. Mesothelial cysts.	Compact. Very fibrous.	Edema and fibrosis in varying degrees. Mesothelial cysts.
Glands	Dilated. Cystic.	Compressed. Atrophic. Fibrosed.	Dilated and cystic, or atrophic. Compressed and fibrotic.
Blood vessels	Dilated. Some thickening in areas. No definite increase.	Vessels thickened. Increased in number. May have thrombosis of arteries, veins, and lymphatics.	Thickening of blood vessels. Considerably increased in number. May have thrombosis.
Cellular infiltration	Eosinophilic infiltration, marked. Few lymphocytes and plasma cells.	Marked infiltration. Lymphocytes, plasma cells, monocytes, histiocytes, fibroblasts, occasional eosinophils.	Considerable number of eosinophils. Moderate or marked infiltration with lymphocytes, monocytes, histiocytes, fibroblasts.
Bone and Periosteum	No change except rarefaction of ethmoid.	Periosteum thickened. Sclerosis of bone. Osteomyelitis.	Thickened periosteum. Some bone sclerosis. Osteomyelitis with severe infection.

suggests that acute or chronic infection has been superimposed upon an allergic state, or in instances where meager secretions are present.

The technic of obtaining and preparing secretions for cytologic examination can be summarized as follows: Specimens should be taken from both nasal passages. These may be obtained by blowing

the nose on waxed paper or into a glass receptacle or on a glass slide. If no secretion can be obtained by blowing, then secretions may be obtained with an applicator or stimulated by inserting a saline tampon into the nasal passages. Secretions from the sinuses may be obtained by puncture or washing. A thin serous discharge will show a sufficient number of eosinophils for identification, and a mucoid discharge usually reveals large quantities of eosinophils. Secretions are more likely to show many eosinophils immediately after an acute exacerbation of symptoms, due to migration of eosinophils through the epithelial layers.

The interpretation of the cytology of the secretions rests with the individual worker. The nature and character of the clinical history, the nasal changes, the presence or absence of infection, and the amount of secretion must be taken into consideration. There is no minimum diagnostic percentage of eosinophils. The interpretation must be made after careful consideration of other pertinent clinical findings. Repeated smears are essential.

A predominance of eosinophils on more than one occasion is highly suggestive of the presence of allergy. Repeated smears in which there is a predominance of neutrophils indicate an acute or chronic infection. In patients with nasal polyps, the greatest degree of stagnation with secondary infection occurs, and necessarily there is some increase in the number of neutrophils. However, in most instances of nasal polyps, the predominant cell will be the eosinophil. A study of the cytology of the nasal secretions is particularly helpful in patients being treated because, in these instances, the nature of acute exacerbations will determine the immediate future treatment.

Classification of Nasal Allergy

Hansel[1] has suggested that nasal allergy may be classified as follows: Nasal allergy is classified according to *seasonal occurrence:*

1. Seasonal allergic rhinitis
   - A. Hay fever or pollinosis
     - (1) Tree
     - (2) Grass
     - (3) Weed
   - B. Mold allergy
2. Perennial allergic rhinitis
3. Seasonal and perennial allergic rhinitis.

Nasal allergy is classified according to *etiology:*

1. Pollen
2. Mold
3. Epidermal, as animal dander, feathers
4. Miscellaneous inhalants, as orris root, house dust, emanations of insects
5. Food
6. Bacteria
7. Combined types

Nasal allergy is classified according to *pathologic changes:*

1. Gross nasal changes—permanent, transitory, residual
   a. Red type
   b. Pale or simple edema (acute or chronic)
   c. Chronic edematous thickening
   d. Polyposis (acute or chronic)
2. Gross paranasal sinus changes—permanent, transitory, residual
   a. Simple edema (acute or chronic)
   b. Chronic edematous thickening
   c. Polyposis (acute or chronic)

Nasal allergy is classified according to *associated allergic clinical states:*

1. Respiratory allergy, as bronchial asthma and bronchitis
2. Gastro-intestinal allergy
3. Cerebral allergy, as allergic headache
4. Cutaneous allergy
   Eczema, urticaria, angioneurotic edema
5. Drug allergy
6. Contact dermatitis
   Local or systemic

Nasal allergy is classified according to complications of *acute and chronic infection and nonspecific and associated nonallergic states.*

The Clinical Course and Symptomatology

The onset of nasal and paranasal allergy may be gradual or sudden, depending upon the nature of the etiologic factors and the intrinsic and extrinsic factors. The onset may be influenced by acute and chronic infections, acute infectious diseases of childhood such as measles, scarlet fever, or whooping cough, operations upon the ear, nose and throat, major operative measures, anesthesia, injections of therapeutic sera, occupational and environmental contacts such as undue exposure to allergens and certain general conditions as puberty, menses, pregnancy, menopause, or physical or psychic shock.

The clinical course of the symptoms is influenced by acute and chronic infections and the amount of discomfort is influenced by the

anatomic or pathologic anatomic conditions of the nasal passages and paranasal sinuses such as deflected septa, narrow, small nasal passages, adenoid tissue, chronic edematous mucous membranes, polyps which produce obstruction, stagnation, and infection superimposed on the allergic state.

The clinical course may be prolonged or brief, the allergy may disappear following therapy, or more rarely it may clear up spontaneously. On the other hand, it may disappear, only to be exhibited as another clinical manifestation of allergy. When acute or chronic infection is superimposed, the clinical course may become much more severe, and therapy may be a very difficult problem.

The nasal symptoms of allergy are:

Sneezing
Itching
Nasal obstruction (stuffiness, sense of fullness, and congestion)
Nasal discharge
Loss of sense of smell
Headache

Other symptoms of allied allergic manifestations may be present.

Gross Pathologic Changes

The gross pathologic changes in the nasal passages which are observed upon examination are dependent primarily upon the extent, amount, and duration of edema. The edema is seldom uniform throughout the nose except in acute exacerbations of symptoms. It is more marked along the lower edge of the middle turbinate, in the middle meatus, sometimes on the anterior end of the inferior turbinate, and over the tubercle of the septum. In patients with continuous allergic reactions, the changes are more likely to be widely and fairly uniformly distributed, and the tissues appear to be boggy and covered with serous nasal discharge. During periods of quiescence, the edema tends to resorb. Pathologic changes may be transitory, permanent, or residual.

Chronic symptoms result, in most instances, in thickening of the tissues due to edema and the occurrence of polyps. Marked pathologic changes of a permanent nature are usually bilateral and are confined to certain regions of the nose. This is dependent upon two factors: First, predisposition of the nasal mucous membrane to edema is largely controlled by its histologic structure and, in this respect, the mucous membrane covering the structures in the middle and superior meatus has a more delicate supporting stroma than is found in other tissues of the nose. Secondly, the inspiratory zone determines the location of the most marked changes. The middle meatus is, therefore, subject to the greatest degree of irritation, both from specific allergens and from nonspecific agents. The areas for most marked pathologic

changes are (1) on the edges of the meatus semilunares, (2) in the infundibulum, (3) at the ethmoid ostia, (4) at the ostium frontale, (5) at the ostium maxillare, (6) on the edge of the middle turbinate, (7) on the edges of the accessory furrows of the middle turbinate, (8) on the ethmoid bulla, and (9) in the ethmoid cells. The degree of edema and pathologic change is dependent upon the severity of active symptoms, the stagnation of secretions present, particularly purulent secretion, and the presence of superimposed infections. During periods of quiescence, either spontaneous or under therapy, small or medium sized polyps may disappear. On the contrary, during acute infections, inflammatory edema is superimposed and swelling is greater.

In the paranasal sinuses, gross pathologic changes, except for those in the ethmoid area, must be determined by means other than rhinologic examination. It is well to bear in mind that in allergic states of the nasal passages, corresponding changes of similar degree appear in the paranasal sinuses. In the majority of instances, roentgen examination with or without lipiodol will determine the extent of involvement.

Mucous polyps are considered by many workers to be primarily influenced by the allergic condition of the nose and paranasal sinuses. Kern and Schenck[4] have found the clinical incidence of mucous polyps in allergic conditions to be 26.5 per cent as shown in the following table:

TABLE 2

CLINICAL INCIDENCE OF MUCOUS POLYPS IN ALLERGIC CASES
(Kern and Schenck)

	Total Cases	*No. with polyps*	*Per cent*
Bronchial asthma	600	183	30.5
Vasomotor rhinitis	104	15	14.4
Hay fever (seasonal)	118	16	13.5
Hay fever and perennial asthma	52	18	34.6
	874	232	Av. 23.2

The incidence of mucous polyps in routine examination of patients with nonallergic disease as a major complaint is shown in Table 3.

TABLE 3

INCIDENCE OF MUCOUS POLYPS IN ROUTINE EXAMINATION OF PATIENTS WITH NONALLERGIC DISEASE AS MAJOR COMPLAINT

Presenting disease	*Total Cases*	*No. with nasal polyps*
Bronchiectasis	73	1
Lung abscess	17	0
Pulmonary tuberculosis	82	6
Arthritis	200	7

In patients who complained chiefly of nasal polyps, the incidence of allergy is shown in Table 4.

TABLE 4

Total number of cases	25	
Personal allergy discovered in	22	
Familial allergy found in	20	
Positive skin tests found in	17	(2 negative; 6 not tested)
Entirely negative for allergy	1	(on section found to be papillary hypertrophy, not mucous polyp)

Kern and Schenck reached the following conclusions regarding the relationship between allergy and nasal polyps.

I. Mucous polyps are extremely common in allergic conditions of the respiratory tract.

II. In patients with presenting symptoms of nonallergic diseases of the respiratory tract, mucous polyps are comparatively rare, even in the presence of extensive and chronic sinus infection.

III. All patients with mucous polyps have been found to have a personal history of allergy.

IV. Mucous polyps occur particularly in those types of respiratory allergy that are protracted and perennial, suggested that a bacterial factor is present.

V. The rôle of bacteria in the production of polyps is uncertain; it is suggested that true hypersensitiveness to bacteria is the usual mechanism.

VI. The treatment of patients with mucous polyps must include attention to the allergic factor; the failure to reckon with this factor is the prime cause for the postoperative recurrence of the condition.

DIAGNOSIS

As a rule, a definite diagnosis of nasal allergy can be made on the basis of symptomatology and careful intranasal examination. However, instances occur in which neither a careful evaluation of the symptomatology nor the gross pathologic changes are sufficiently characteristic to definitely establish a diagnosis. Therefore, certain clinical and laboratory data are necessary in order to prove or rule out the presence of allergy, and also to determine other factors which may influence the onset and the clinical course of the disease. We suggest that the following characteristics of allergy be considered in the routine diagnosis and investigation of all patients with nasal allergy.

1. A positive family history of allergy. This has been found in from 60 to 70 per cent of the cases.

2. Past and present history of other manifestations of allergy.

3. The nose and paranasal sinuses.
   a. Nasal symptoms, sneezing, itching, serous or mucoid discharge, obstruction.
   b. Changes in mucosa, pallor, edema, polyps.
   c. Secretions—eosinophilia.
   d. Roentgen examination positive—edema, polyps, retained secretion.
   e. Histopathology—edema, eosinophilic infiltration.
4. Skin reactions—positive in 80 per cent of cases.
5. Blood eosinophilia.
6. Complications.
   a. Acute and chronic infections
   b. Non-specific factors.

The cardinal characteristic findings of nasal allergy cannot be demonstrated in every instance but in only a few cases will the investigator fail to find the characteristics listed under headings 3, 4, and 5. In a definite percentage of cases, a history of family and personal manifestations of allergy will not be elicited. This, however, does not preclude the possibility of allergy. The symptomatology and the characteristic clinical and laboratory findings are of greater importance than the history in the doubtful cases. It is obvious that complete studies are necessary.

Investigation of the Patient with Allergy

The following table summarizes the investigations in making a diagnosis of allergy:

Table 5

Investigation of the Allergic Patient

History—personal, family, allied conditions
Physical examination—special examinations as indicated by history and physical examination
Laboratory studies
  Cytology of secretion
  Biopsy of tissues, histopathologic picture
  Blood studies—digestive leukocyte response, blood eosinophilia, red blood cell sedimentation rate, blood chemistry
  Bacteriologic studies—secretions, sputum, stool
  Roentgen studies—sinuses, chest, gastro-intestinal tract, kidneys, ureters, bladder, skull
  General studies—gastric analysis, basal metabolism, hormone assays
Protein tests
  Scratch, intracutaneous, passive transfer, intra-ocular, intranasal, patch
Diets, elimination; food diary
Avoidance of common inhalants

Confusing ideas concerning investigation of the patient with allergy occasionally occur. Often some skin tests are substituted for a complete and thorough study. In no way does this imply that allergy

is correctly investigated. When the investigator completes his study, he should be able to answer all the criteria established by Hansel under the classification of nasal allergy, namely, the seasonal occurrence of symptoms, the etiology, whether due to pollens, molds, epidermals, miscellaneous inhalants, foods, bacteria or a combination of these, the gross nasal and paranasal changes, the associated manifestations of allergy, the complications, whether by acute or chronic infection, and any associated nonallergic states.

In the investigation of the patient with nasal allergy, we have established the following phases of study:

Personal history, family history, allied conditions: One learns that a careful clinical history is the most important procedure in the diagnostic survey. Through this, one may first ascertain whether or not the patient is an allergic individual. Such information is strengthened by finding a strong family history of allergy. In a consecutive series of 166 cases of nasal allergy, we were able to elicit a family history in 120 cases or 72 per cent. A history of associated manifestations of allergy is important. In this same series of 166 patients with nasal allergy, we obtained a history of other allergic phenomenon of clinical importance in 84 or 50.6 per cent. The history must be very complete, not only in regard to the suspected allergic state but to any condition that may alter the patient's health from normal. Failure to evaluate the importance of associated disorders results in poor relief of symptoms; this is particularly true in the presence of metabolic disorders, glandular dysfunction, focal and systemic infections.

Physical Examination: In our cases, a physical examination is made routinely. This consumes a brief period of time and occasionally some further clue is noted as to the true nature of the problem. More than this, the investigator is assured of the absence of organic disturbances in most instances and, where questionable, further special investigation will prove or disprove the presence of organic pathology. The necessity for special examinations will be indicated by a careful physical examination.

Laboratory Tests: Routinely in our work at the Clinic, complete blood counts, estimation of the blood sugar, the Wassermann reaction, and urinalysis are carried out. In addition to these tests, blood eosinophilia, cytology studies of the secretions of the nose and sinuses, and the sedimentation rate of the erythrocytes are of greatest value. In the 166 cases cited, blood eosinophilia of greater than 3 per cent was found in 62 per cent of the patients. The average eosinophil count was 6 per cent. This observation was based, as a rule, upon one determination for eosinophils. Previously, the importance of careful

examination of nasal secretions was discussed. This is one of the most valuable of laboratory procedures. In many instances, where it is difficult to determine the influence of allergy and infection in the production of nasal symptoms, this single laboratory procedure will prove of value in definitely establishing the factor of allergy or infection or a combination of the two. The entire procedure is simple and if the results secured by study of the nasal smears are interpreted in the light of careful history, thorough clinical examination, and other laboratory findings, very few errors will be made in diagnosis.

The third laboratory procedure of value in determining the factors of infection and allergy in nasal and paranasal sinus problems is the sedimentation rate of the erythrocytes. We have used the method of Rourke and Ernstene which we believe is the most accurate. In pure uncomplicated allergy, there is no increase in the sedimentation rate of the erythrocytes as shown by determinations we have made in more than 1,000 patients with allergy of the upper respiratory tract. Where acute or chronic infection complicates the picture, there is definite increase of the sedimentation rate, which is proportionate to the acuteness and severity of the infection. This is greatly increased if purulent material is retained in a sinus cavity and drainage is not established. We believe this laboratory test is of as great significance as the cytology studies of nasal secretions in establishing definitely the presence or absence of infection in nasal problems, and if present, the severity and extent of infection.

Roentgen Studies: Very comprehensive studies have been made by a number of observers in the comparison of transillumination and roentgen examination of the sinuses in allergy of the nose and paranasal sinuses. The general consensus of opinion has been that the roentgen examination gives better results. It is generally agreed that transillumination is usually ineffective in showing the presence of edematous mucous membranes and polyps in the antra because of the tendency of these tissues to transmit light. In our experience, this has been borne out in several instances, although in the majority of cases, findings by transillumination and roentgen examination have agreed.

Kern and Schenck[5], Kern and Donnally[6], Baum[2] and Hansel[1] found upon reviewing large series of cases which totaled more than 1,000 that positive roentgen evidence was secured in 90 per cent of the patients with active symptoms of respiratory allergy. Hansel made roentgen examinations of 56 children with active symptoms of allergy and found the sinuses to be clear in only three. The cloudiness was confined chiefly to the antrum and the ethmoids. In 13 selected cases of this group, the antra were punctured and washed. The washings were clear in five; they contained mucus in three and purulent material in five.

Our experience with roentgen examination of patients who have respiratory allergy with active symptoms differs from that of Hansel and other workers in the percentage of positive findings. We recognize that clouding of the sinuses, particularly of the antra and the ethmoids, occurs in severe allergic reactions of the upper respiratory tract. In a series of more than 300 cases, we were able to obtain positive findings in about one-third of the cases. In the group demonstrating positive roentgen findings, a small percentage of the patients were found to have some active infection, although a primary allergic reaction existed.

The limitations of the roentgen examination as a single factor in making a diagnosis should be realized and a diagnosis should never be made from the roentgen evidence alone. When roentgen findings are carefully correlated with the clinical history and other laboratory data, especially those concerning the cytologic and bacteriologic analyses of the secretions from the nose and paranasal sinuses, they may be evaluated more accurately. The transitory nature of the edema which occurs in the mucosa of the paranasal sinuses in allergy adds to the unreliability of the roentgen examination in establishing a diagnosis. Marked changes, as indicated by roentgen studies at one time, may be absent at a repeated examination when the active symptoms of allergy subside. Repeated examination with and without lipiodol are often necessary to determine the extent of chronic or permanent changes in paranasal sinuses.

Studies of the *bacteriology* of the secretions of the nose and paranasal sinuses have been confined largely to the identification of the organisms and the preparation of autogenous antigens to be used as therapeutic aids. Where definite infection exists or where some of the symptoms appear to be due to bacterial allergy, autogenous vaccines are made and tested intracutaneously. Oftentimes, antigens made from secretions fail to cause any striking skin reactions. These are discarded and fresh specimens are obtained for further preparation and this procedure is continued until antigens are secured which give both excellent skin reaction and some focal reaction. The interpretation of the skin test with the bacterial antigens depends not so much on the immediate urticarial wheal type of skin response as noted in true atopic reactions, but in the erythematous, inflammatory type of reaction, as noted in the tuberculin reactions. These reactions are noted in 12, 18, 24, and 48 hours after the time of injection of the antigen.

Studies of the *blood chemistry* other than determinations of the blood sugar are rarely made unless they are indicated by the presence of clinical problems of a nonallergic nature. In a series of determinations for serum calcium and phosphorus, we have never encountered a single deviation from the normal that could be attributed to allergy.

Special laboratory tests are carried out if indicated by the clinical history and examination. Determinations of the basal metabolic rate have been used most frequently and with more apparent value. In our experience, one-third of the patients exhibit either hypometabolism or true hypothyroidism. Hypometabolism, which is common in respiratory allergic states, responds well to thyroid medication and, as the hypometabolism approaches a normal state, lessening of the dosage can be effected and finally discontinued.

In several hundred patients, determinations of *gastric acidity* have been made, and there has been no more deviation from the normal than would be expected in an average group of patients with any type of problem.

Finally, it is to be remembered that the histopathology of allergy is a very definite picture. In problems where diagnosis cannot be established by other measures or where tissues for pathologic examination can be secured without difficulty, specimens should be taken. There can be no mistake in diagnosis when the histopathology of allergy is studied.

Allergy Tests

From the foregoing discussion, it is obvious that we consider allergy tests as only a part of the investigation of the patient's problem. Each patient must be individualized and several methods of skin testing may necessarily be used in the same patient. In the majority of patients with respiratory allergy, the scratch method is employed first. This insures against the possibility of constitutional reactions which are discouraging both to the patient and the physician. In a small percentage of patients, allergic reactions will be of sufficient severity that this type of testing is satisfactory; however, in the majority of cases, further investigation is necessary and then the intracutaneous method is employed. This is particularly true if the patients do not have pollen allergy. We have found that at least three dilutions of each allergen are necessary in intracutaneous testing. For the chronic low grade allergy, and particularly where refractive types of skin are encountered, we have used the undiluted stock solutions, except in pollen allergy where tests are always by the scratch method. The majority of patients respond best to the 1:10 dilutions of the regular stock or undiluted antigens. For patients with a more acute and easily elicited response to allergens, complete series of antigens are used with 1:100 and 1:1000 dilutions. If the proper dilution is selected for each patient, skin reactions are easily elicited and interpretation of reactions is not difficult. Through this method of individualizing the tests for each patient, we have obtained much more satisfactory responses from the skin tests and have secured a higher percentage of excellent clinical relief.

The third method of testing for allergens is the passive transfer as elaborated by Prausnitz-Küstner. The indirect method of testing is necessary where the following conditions exist:

1. In children where physical and mental shock render direct methods of testing inadvisable.

2. In patients with severe cutaneous lesions where extensive involvement and lichenification of the skin renders sites for testing impossible.

3. In the group of patients who present a generalized hypersensitive, nonspecific response to any substance applied. This response probably is due to trauma and release of histamine-like bodies locally and is not infrequently seen in cases of eczema and urticaria.

4. In the acutely ill patient.

During the past four years we have used the passive transfer method for complete allergy tests in more than 300 patients and the clinical results have been comparable or superior to the direct method of testing. Briefly, the method is as follows: Under sterile precautions, 30 cc. of blood is withdrawn by venipuncture. The blood is centrifuged under sterile precautions and the serum drawn off. No filtering for sterilization is needed if sterile precautions are observed throughout the procedure. Using quantities of one-fourth to one-third cc. for each site, the undiluted serum is injected intracutaneously into a professional test person. By means of tests, history, and examination, this individual has previously been proved to be nonallergic. *A relative of a patient is never used.* These sites, which usually number from 32 to 48, are marked by making a linear skin incision with a sharp scalpel. At the end of 48 or 72 hours, the sites are used for testing by the intracutaneous method. If a sharp reaction occurs at a site, it is not used for further testing because the reagins present in this site will have been exhausted. By repeatedly going over the sites, after 48 hours have elapsed between tests in order that antigens may be absorbed, one is able to make from 80 to 100 tests which, if judiciously selected after careful history, will suffice in most instances for a complete allergy examination.

Ophthalmic and intranasal tests have their place in the allergic survey in the hands of most workers. These are performed by simply placing in the conjunctiva or blowing against the nasal mucosa small quantities of purified dried powder of the substance that is suspected. If hypersensitivity exists, an immediate reaction is noted, and the substance can readily be washed out with normal saline and weak solutions of adrenalin. Often a severe reaction occurs which may be discomforting to the patient for a few days. Because of this undesirable reaction and because testing by scratch, intracutaneous, and passive

transfer methods are reliable in respiratory allergy, we have not employed ophthalmic and intranasal tests.

The fallibility of determining allergens by skin testing has received considerable criticism from time to time. In most instances, this has been stimulated by the failure to identify causative agents, and the number of false positive reactions that are encountered occasionally. Undoubtedly, skin tests are not accurate in 100 per cent of the cases, but it is true that skin testing, in the hands of an experienced worker who uses reliable and potent extracts, gives a working knowledge of the problem which cannot be paralleled by any known diagnostic procedure. In respiratory allergy, skin tests give the most accurate results, being reliably correct in 90 per cent of the patients.

Finally, one may use all three methods of testing for allergens in order to obtain sufficient information. Seldom does this combination of methods result in failure, but if such an instance occurs where food allergy is suspected, further investigation through food diary, elimination diets of individual or stock type, and the use of the digestive leukocyte response, as recommended by Vaughn[7], gives information which is of undeniable value.

Allergens

Any protein substance may be allergenic. In Table 6 a summary is given of allergens known to produce at least 95 per cent of allergic reactions. Pollens of trees, grasses, and weeds rank as the largest factors in the production of respiratory allergy.

Table 6

Allergens

Inhalants	
Pollens	Tree, grass, weed—occasionally flowering plants.
Molds	Chiefly families of alternaria, aspergillus, cephalothecium, hormodendrum, monilia, penicillium.
Epidermals	Feathers, animal dander
Miscellaneous	Flaxseed, glue, orris, pyrethrum, silk, kapok seed, cottonseed, tobacco, emanations of insects, Indian gum, house dust.
Ingestants	Food, bacteria, drugs, molds
Cutaneous	Animal or plant protein drugs
Parenteral	Sera, toxins, viruses, drugs
Intrinsic	Infections
Ill-defined	Smoke, odors, vapors

Second to the pollens, epidermal substances are considered by many workers to be the largest factor. However, since the advent of mold allergy, many patients with both seasonal and perennial nasal symptoms

have been found to be sensitive to mold and with the large factor that house dust plays, this group of etiologic factors threatens the place of the epidermal substance as the second most common cause of respiratory allergy. All workers in allergy recognize the importance of house dust allergy in patients who suffer with a distinct seasonal respiratory allergy or an intensification of a perennial respiratory allergy in the winter season. This is particularly true where contact with house dust is imminent as in those domestically employed.

Occasionally, patients with allergy have intense reactions to one of the miscellaneous substances other than house dust; this is particularly true of animal epidermals, silk, kapok seed, cottonseed, and orris root. In these instances, such a single intense reaction may well be the major factor in the production of symptoms, and immunization therapy usually gives excellent results.

Bacterial allergy is a prominent factor where allergy and infection have existed in the nasal passages and paranasal sinuses. We have used stock bacterial vaccines in skin testing in these cases, but our findings show that autogenous antigens are by far superior to the stock vaccines. In every patient where infection is superimposed upon allergy, secretions, either nasal, sinus, or bronchial, are secured for preparation of autogenous vaccines. Although seldom the major factor in the production of allergic reactions, therapy with bacterial vaccine in carefully chosen cases has been of distinct value.

Food allergy is a distinct factor in the production of respiratory allergy. Although many of our patients have definite allergy to inhalants and bacteria, the majority have sufficient food allergy to require strict dietary management. Grains, particularly wheat, and milk and eggs, in the order given, are most important. The investigator should never overlook this important phase of food sensitiveness in the study of any patient with respiratory allergy despite the fact that severe reactions are obtained to the inhalants.

Differential Diagnosis

Common conditions of the nose that must be differentiated from allergy are frequent colds, acute rhinitis and sinusitis, hypertrophic rhinitis, chronic sinusitis, chronic sinusitis in sinus chest diseases, chronic nasal discharge and headaches, lues, headache with nasal obstruction, and pallor of the mucous membrane due to poisoning from coal tar products.

Other conditions such as severe secondary anemia, hypothyroidism, states of malnutrition and deficiency disease may result in vascular disturbances with changes in color of the nasal mucous membrane, suggesting primarily an allergic state.

It is well known that deflected septa produce chronic nasal obstruction and increased nasal secretion. Physical agents, such as gas, smoke, fumes, mechanical and chemical irritants, atmospheric conditions with extremes and sudden changes of temperature, winter weather with enforced residence in buildings where breathing of dry, unhumidified air and contact with coal smoke and coal dust is unavoidable for prolonged periods of time without proper ventilation and air conditioning, produce exacerbation of nasal symptoms which may simulate allergy. Nasal allergy is often a basis or an aggravating factor in manifesting or prolonging these conditions, but careful history and examination will prove the presence or absence of allergy.

In patients who complain of chronic nasal obstruction and discharge and in whom chronic thickening of the nasal mucous membranes and polyposis with suppurative processes are noted, the possibility of a primary allergic condition must be considered. Hyperplastic ethmoiditis, chronic edema, and polyposis of the sinuses must be looked upon as allergic in origin until proved otherwise. Repeated clinical examinations of nasal secretions and detailed survey of the history should be made before the presence of allergy is excluded. It should be kept in mind that cerebrospinal rhinorrhea may rarely be encountered in patients with profuse watery discharge from the nose, and differentiations can be made by a chemical examination of the nasal secretion.

Mulberry hypertrophy of the posterior tips of the inferior turbinates can be distinguished from nasal polyps by their location, which is usually in the middle meatus.

The possibility of malignant tumors of the carcinoma type should be kept in mind when the process is unilateral and pain and bleeding are present.

Treatment

Correct diagnosis is imperative in order to institute proper therapeutic measures. It is discouraging to treat a patient for nasal allergy if he is actually suffering with an acute or chronic infectious involvement of the nose and paranasal sinuses.

With the diagnosis correctly made, the next survey includes knowledge as to the adequacy of clinical investigation. No short cut to diagnosis is possible in any patient and each problem deserves the thorough investigation that has been reviewed in the preceding pages. Careful study will accord patients with respiratory allergy such excellent clinical relief as to insure the permanency of allergy in the field of therapeutic medicine.

In our experience, one of the greatest causes for failure to obtain reasonable clinical success in patients who are definitely allergic is not

due entirely to inadequate investigation, but to the failure of the physician to convey to the patient the understanding of allergic reactions, of allergenic substances, and what is to be done about them. This phase of the program demands time and detail on the part of both the patient and the physician. We give not only complete verbal instructions, but also carefully written instructions in an attempt to educate the patient in regard to the meaning of allergy and the necessary care and consideration that is a feature in the proper therapy of every problem. A satisfactory allergy regimen and control cannot be accomplished unless this policy is strictly adhered to.

Allergens which can be avoided or eliminated: As a rule the common inhalants, with the exception of pollens and molds, can be avoided unless the patient is extremely sensitive. When inhalation allergy is proved to be of distant clinical importance and elimination is not possible, immunization therapy is necessary.

If the patient is allergic to food, only simple elimination is necessary. Desensitization to foods, either oral or parenteral, is not practical or helpful. In making substitutions in the diet, special attention must be given to assure a diet that is adequate, nutritious, and palatable. We employ not only the physician's knowledge of this, but also the cooperation of our Dietetic Department. Where major foods are eliminated, it is desirable not only to rearrange the diet according to the permitted foods, but to give additional vitamins A, B, and D, and calcium. We feel that this insures against disturbances of nutrition and often is of value in maintaining the physical well being of the patient. The length of time that foods must be avoided is dependent upon the individual patient and his symptoms. It is reasonable that no food which has definitely been proved to be a specific factor should be returned to the diet in less than six months. The program to be followed in each particular case can be determined only by experience.

Allergens which cannot be avoided or eliminated: Sensitivity to pollens of trees, grasses, weeds, and occasionally to pollens of flowering plants necessitate hyposensitization. It is recognized and accepted that pollen allergy can be adequately treated by hyposensitization with satisfactory relief in 90 per cent of the cases. Of the three methods of therapy—coseasonal, preseasonal, and perennial—we feel that the perennial method is the most satisfactory and gives a high percentage of relief in the majority of patients.

Allergy to house dust and mold, particularly if there is a distinct variation during the winter season, demands immunization therapy if clinical symptoms are persistent and annoying. The necessity of immunization with house dust antigens can be determined by eliciting

a careful history of symptoms on exposure to dust and by interpreting the degree of skin reaction to house dust antigens. Mold allergy is a distinct and large factor in perennial respiratory allergy. If its significance in the problem is firmly established, immunization therapy is necessary.

Occasionally, patients with respiratory allergy are extremely sensitive to one of the inhalant allergens other than dust, mold, or pollen. These are orris root, silk, epidermals, kapok seed, cottonseed, and emanations of insects. Immunization in this group practically always affords excellent relief.

Previously, a discussion of bacterial antigens and bacterial vaccine therapy was given. We have used only autogenous vaccines and found this phase of therapy to be a valuable adjunct if treatment is continued over an extended period of time.

In hyposensitization therapy it should be emphasized that doses of antigens should not be large enough to produce too great local reaction and never symptoms of a constitutional reaction. It is obvious that signs and symptoms of systemic reaction are evidence of shocking tissues and not stimulating immunity. This particular principle has a counterpart in that it renders any type of immunization treatment a long and tedious process. In immunization therapy, it is best to consider measures that may last several years.

General measures in treatment: The commonly associated nonallergic states are hypometabolism or true hypothyroidism and mild hypochromic anemia. Occasionally, a patient has a nutritional deficiency which is either due to enforced dietary restrictions or failure to assimilate ingested food substances due to the marked allergic state. This is not uncommon in patients with food allergy. The general measures most commonly employed with these patients are control of the hypometabolism or true hypothyroidism with small doses of thyroid and control of the secondary anemia.

We study all patients carefully from the viewpoint of any general disturbance and if such a disturbance is present, treatment is given as indicated by the problem involved.

Nonoperative treatment of the nasal passages: Definite allergy of the nasal passages often is complicated by pathologic conditions such as badly deflected septa, nasal spurs, nasal polypi, polypoid degeneration of the turbinates, or sinusitis. Conservative measures are indicated in these problems until the allergy is controlled. These membranes are hypersensitive and the use of drugs usually does not result in any relief but only adds to the irritation and congestion and the amount of edema. In the presence of such pathologic conditions, conservative treatment should be instituted in order to secure drainage of

any purulent material in the sinus areas or the nasal passages. If treatment is required, only mild drugs should be used. We have found weak solutions of ephedrine, neosynephrin hydrochloride, and cocaine to be most satisfactory. However, it should be emphasized that unless it is absolutely necessary, local therapy to the nasal passages or the intranasal sinuses should be avoided. If the condition is primarily of allergic origin, proper investigation and therapy will result in satisfactory relief of the nasal problem.

Surgical indications: The surgical indications in diseases of the nasal sinuses and nasal passages in the presence of allergy were discussed by the late Dr. W. V. Mullin[8] in a study of 216 patients who were seen in the Department of Otolaryngology and the Department of Allergy at the Cleveland Clinic. His findings summarize our opinion concerning the diseases of the nasal passages and paranasal sinuses due to allergy. In his group of 216 patients, 52 had had previous operations upon the nasal sinuses but had secured no relief from symptoms. In these 52 patients, no study to determine the presence of allergy had been made. Dr. Mullin found it necessary to carry out surgical measures after the allergic condition was diagnosed and treated in only 16 of these 52 patients. He concluded that in this group of patients careful studies to determine the presence of allergy would have eliminated more than two-thirds of the nasal operations to which these patients had been subjected. In summarizing the 216 cases, Dr. Mullin felt that allergy was a definite factor in the production of nasal and paranasal symptoms in 35 per cent. The importance of primary allergic studies in these patients and the necessity for conservative surgical procedures were emphasized. Further studies in a larger group of patients have led us to believe that the importance of primary allergic investigation in diseases of the nasal passages should not be overlooked, and that a conservative surgical attitude should be continued.

In primary allergic states where pathologic conditions exist that demand surgical measures, the allergy should be completely investigated and a regimen established in which elimination and hyposensitization measures are carried out. This should be continued for a period of two to six weeks before any surgery is undertaken. By this, the edema that is characteristic of allergy will have essentially disappeared, permitting satisfactory surgical results. If surgical measures are undertaken before the allergy is controlled, it has been our experience that a stormy convalescence follows and this is due primarily to the intense edema that takes place after any operative procedure where an active and acute condition of allergy exists. In many problems, we find it necessary to make not only complete allergy investigation and prescribe the proper treatment, but also to institute conservative surgi-

cal measures in order to give the patient complete and satisfactory relief of symptoms. The most sincere cooperation is necessary between the allergist and the otolaryngologist.

In order to insure the permanency of allergy in the field of therapeutic medicine, adequate and thorough investigation of the allergic problem and proper measures of therapy, with consideration of associated nonallergic factors, must be made in every instance.

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EXOPHTHALMOS*

A. D. RUEDEMANN, M.D.

UNILATERAL EXOPHTHALMOS IN CHILDREN

Pyocele: The infection in pyocele usually originates in one of the ethmoids although the antrum may be involved. These youngsters are quite ill, there is an increase in temperature, they have general malaise and complain of pain through the side of the head. Within a short time, signs of increasing congestion, edema of the lids, and some exophthalmos appear. The eye may not be pushed as far forward as it is laterally. There are no changes in the fundus early in the course of the disease but, as the inflammation proceeds, increasing congestion of the veins occurs and later the eye may show a low grade intra-ocular inflammation.

Examination of the nose usually reveals definite clinical evidence of sinusitis. Roentgen examination may show clouding of the sinuses but it rarely shows the orbital entrance or orbital lesion. Use of the suction apparatus is an aid in establishing the diagnosis.

In treating a patient with pyocele, he must first be put at complete rest with heat to the side of the face and eye. The nose must be kept open and constant drainage maintained by the use of suction or irrigation. The orbit should not be incised unless necessary as it is sometimes possible to avoid this procedure. Efforts should be directed toward causing the abscess to localize and, if necessary, the area or a dependent part of the orbit may be incised for drainage. Constant attention must be given to maintaining the integrity of the orbital contents in order to preserve the function. The nasal and supportive treatment must be continued for some time.

Pyemic abscess is a secondary process. The patients usually have had a general infectious disease which has lowered their resistance, and the orbit happens to become the seat of a metastatic infectious thrombosis. The associated exophthalmos is usually directed outward or inward, according to the location of the abscess. Since most of them are outside the muscle cone, the eyeball is not pushed straight out. Associated with this, there may be an increase in the white cell count and a slight elevation of the temperature.

Treatment consists of hot compresses, bed rest, and general measures. If the protrusion is progressive, then the orbit should be incised for drainage.

Orbital cellulitis is a serious inflammation of the retrobulbar tissue due to a foreign body, injury, a metastatic infection or direct extension

*Concluded.

from the sinuses. The lids become red, edematous, and swollen, and the conjunctiva is infected. There is exophthalmos and marked impairment of muscle function with deep boring pain in the orbit. This is a constant dull ache. The infection may be due to any of the usual group of organisms such as Streptococcus or Staphylococcus. Cases are reported in which the B. pyocyanus, typhoid bacillus or Pneumococcus was responsible. Early supportive treatment is essential and in spite of good therapy, 20 per cent of the patients with this condition lose the sight in the affected eye. An abscess may form, causing thrombosis of the central retinal vein, occlusion of the artery, or optic retinitis. The cornea may break down and the entire globe may degenerate in the course of the infection. Meningitis and cavernous sinus thrombosis result in a 17 per cent mortality.

Cavernous sinus thrombosis occurs very infrequently in children and will be discussed under exophthalmos in adults.

Lateral sinus thrombosis has been reported to cause unilateral exophthalmos secondarily. I have never seen exophthalmos but I have seen papilledema. The exophthalmos is a retrograde process and is caused by a general venous stasis which extends over the mastoid bone by way of the emissary veins. These patients are only benefited by treatment of the lateral sinus affection. In cases of papilledema and papillitis, the end result depends upon the time element, the shorter the duration of the involvement of the optic nerve, the better the visual result.

Periostitis: This is not a common disease of children and usually is found only in those suffering from malnutrition and general physical debility. The majority of cases are due to tuberculosis of the lateral wall of the orbit, the inferior outer rim being most frequently involved although the superior margin may be included. The characteristic picture is first hyperemia of the area and this is associated with some swelling and pain. The eyeball is rarely pushed out, usually being displaced inwardly or downward and inward. As the swelling increases, incision will effect drainage of some free pus and probing will lead to uncovered bone. General measures, such as heliotherapy, high calorie, high vitamin diet, and rest are the best measures.

Luetic periostitis (a tertiary leutic process) will produce inflammation, swelling, and pain which usually comes on at night. Luetic periostitis suppurates but rarely in contrast to other types of periostitis, and blood tests on the parents and child are of value in establishing the diagnosis.

Osteitis may be associated with the periostitis and is but rarely seen in the region of the orbit unless some complicating disturbance is present. Necrosis of the bone necessitates its removal and then treat-

ment must be instituted to build up the patient. Attention is called to the possibility in older children of osteomyelitis infiltrating from the frontal sinus into the orbital bones and throughout the walls of the orbit. I have seen several of these cases in which the removal of the bone did not cause much intra-orbital involvement except for congestion and a low grade exophthalmos with some disturbance of muscle balance. To effect a cure, one must be willing to be very radical in the excision of diseased bone; otherwise the process continues to extend.

Tenonitis: Inflammation of Tenon's capsule results in a low grade exophthalmos of only 1 or 2 mm. but the eye is very painful, especially on movement. Any injury to the orbit may institute a low grade tenonitis and penetrating wounds are apt to promote a localized inflammation in the capsule. Here the pain and swelling will be limited and movement of the eye will be painful, especially when the muscle in the area involved is stretched.

Surgical tenonitis subsequent to surgery of the ocular muscles may be very serious, very painful, and is certainly most annoying to the surgeon as well as the patient. This may be caused by irritation from the suture material or an infectious process. Occasionally, slough of the muscle tendon or an unusual amount of scarring will interfere with the desired surgical result.

Foreign bodies may enter the orbit and disappear in the orbital tissue. Small pieces of material usually are lost and, unless they produce signs or symptoms, it is better to do nothing about them. Larger bodies, such as sticks of wood, pieces of copper, and substances that produce an inflammatory reaction must be removed not because of the exophthalmos but because the secondary reaction may produce fixation of the muscles, diplopia, or deep cellulitis.

Noninflammatory

Spontaneous hemorrhage into the orbit is very rare but may occur in association with scurvy, leukemia, or any severe blood dyscrasia. Trauma at birth or later does not occur commonly and the protrusion in any event is not great. I recently saw a case in which severe exophthalmos occurred in malignant hypertension due to hemorrhage following rupture of the orbital portion of the ophthalmic artery.

A diagnosis of *intermittent (vascular) exophthalmos* due to varices of the orbital vessels, telangiectasis or vascular tumors such as angiomata or lymphangiomata is very difficult to establish. It is sometimes of value to have the patient bend over sharply so that there is increase in the venous stasis and a secondary increase in the exophthalmos. An increase in size may occur while straining, crying, and,

in some instances, during the menstrual period. These changes are slowly progressive and, when the eye is definitely moving forward, the tumor should be removed.

Encephalocele is a congenital defect which does not produce much exophthalmos as a rule, but it displaces the eyeball downward and outward. The bony dehiscence is between the ethmoid and frontal bones, and it is sometimes possible to demonstrate this by roentgen examination. The cyst is soft and may be pressed out. The mass may be replaced and the opening covered by a bony plate.

Meningocele is a congenital condition which is very rare. It occurs at the same location as an encephalocele, is more soft, and may pulsate. It must be differentiated from encephalocele and dermoid cyst. Roentgen examination and aspiration with a large bore needle will aid in the diagnosis. The cyst produces little or no exophthalmos but moves the eye downward and outward. Extreme care must be exercised in the management of these conditions because of the danger of meningitis.

Recently I saw a patient who had been in an accident and had a large cyst in the upper inner angle. There was some protrusion and considerable malposition of the globe. The preliminary diagnosis was pyocele extending inward from the anterior ethmoids. Dr. Paul M. Moore of the Department of Otolaryngology proposed to exenerate these cells but fluid obtained through an incision showed the cyst to extend into the orbit. Further exploration and excision showed a cystic degeneration of the dome of the lachrymal sac which had been cut off at the time of the accident and displaced upward and inward. Removal resulted in complete recovery.

Dermoid cysts rarely produce exophthalmos as they are usually superficial, extending upward and outward, and although they may push the eye downward and inward, exophthalmos is not a common finding. They are congenital and contain exfoliated epithelium, hair, oil and rarely teeth. Removal is indicated for cosmetic reasons and because of the exophthalmos.

Teratoid cysts or teratomas occur but rarely and usually they contain more tissue than do the dermoids. They also are congenital and may continue to develop. Parts of a fetus have been found and a case is on record of one teratoid growth which was made up of an almost complete fetus. There are cysts due to old hemorrhages, and a rare cyst of the trochlear of the superior oblique.

Thyroid disease occurs in children and as noted in the discussion of bilateral exophthalmos, it produces exophthalmos fairly frequently. This usually is bilateral and any unilateral exophthalmos may be relative because of the unequal widening of the palpebral fissures.

The latter sign occurs earlier than true exophthalmos and disappears rapidly following treatment of the thyroid disease. Progressive exophthalmos as proved by measurements requires surgery of the thyroid gland. Care of the eyes should be taken to prevent ulceration due to exposure. The longer the exophthalmos has been present, the less recession may be obtained and the more difficult becomes the problem of reëstablishing normal ocular muscle balance and position of the eyes.

Tumors of the orbit in children are rare and of mixed types. Vascular tumors have been discussed under intermittent exophthalmos. Sarcomata, either round or spindle cell, occur and these either extend back along the nerve or in or around the nerve itself. Any connective tissue in the orbit may give rise to a sarcoma. These tumors may cause little or no exophthalmos for a long while, but they usually produce loss of vision early if they arise in the muscle cone. The exophthalmos, because the tumor is inside the muscle cone, is straight forward. The usual sarcoma is round, soft, and encapsulated, and may cause any type of protrusion.

Mucoceles are rare and because of their anlage in bone they invade the orbit. The exophthalmos usually is not straight forward.

Rarely are *brain tumors* allowed to progress so long that they extend into the orbit. Tumors of the anterior lobe or tumors in the middle fossa may obstruct the venous outflow and produce a secondary orbital edema.

Congenital malformations are apt to produce an exophthalmos. Maldevelopment of one side of the head may produce a relative exophthalmos on the unaffected side. An enophthalmic eye may cause the normal side to have the appearance of exophthalmos. The cases of "Türmshadel," "Spitzkopf" (oxycephaly) or "tower skull" may be associated with a serious type of unilateral exophthalmos. A prominent eye or eyes may be accompanied by many varying degrees of changes in the skull, and the appearance of the patient is apt to be grotesque. He is uncomfortable because of the muscle error and exposure and sees poorly because of the optic atrophy, so that he usually is an unhappy individual. Hydrocephalus, as a rule, does not produce exophthalmos.

Unilateral Exophthalmos in Adults

An adult is more prone to unilateral exophthalmos than is a youngster. The danger of trauma is greater, and because of his additional years, he has accumulated pathological processes and physical debilities which now begin to exact their toll.

Various blood dyscrasias may result in a *spontaneous hemorrhage* of the orbit which will produce an acute exophthalmos. This usually

is not very great, being 2 to 3 mm. and if the general process is controlled, a normal position of the eye and normal function may be recovered. However, the hemorrhage may not resolve very slowly and blindness may ensue or a blood cyst be formed.

Arteriovascular disease with or without hypertension may produce hemorrhages of the orbit which vary in size and extent. The resulting exophthalmos may be small or great according to the location of the hemorrhage and the amount of blood lost. Outside the muscle cone, the blood suffuses anteriorly and may appear in the lids and ocular conjunctiva. Hot compresses, bed rest, and a pressure bandage should be prescribed and general measures should be directed toward reducing the blood pressure.

Asphyxia, especially where there has been violent coughing and choking, may result in an orbital hemorrhage. This is usually associated with intra-ocular and conjunctival hemorrhages. Severe compressing injuries of the chest may also produce ocular hemorrhage. When crushing blows are received in which a heavy weight or pressure suddenly compresses the wall of the chest even though it may rebound without fracture, the exerted pressure may be transmitted throughout the vascular system and the vessels cannot compensate for the sudden mechanical pressure. The hemorrhages will be present in the retinae.

Scurvy and other deficiency diseases that change the blood volume may result in orbital hemorrhage. Today, scurvy in this country is very uncommon, although the possibility of its occurrence must be borne in mind, especially when dealing with adults who have decided how they should eat and with faddists who believe they know how to eat.

The *inflammatory processes* which cause increase in the orbital content are numerous. The orbit is well located for protection but unfortunately man insists on exposing himself to many undue risks. The cushioning effect of the air cells around the orbit are a boomerang when they become infected. In spite of this the orbit is only infrequently involved, considering the number of injuries to the head and infections of the sinuses. Probably more cases of slight exophthalmos are seen than are recorded, but evidently the eyes recover their normal function and position. It is only when noticeable and when exophthalmos is associated with pain and disturbances of function that the oculist is consulted as to the cause and effect of the existing condition. The infectious processes are the same as in children with some increase in the number of the following conditions.

Fortunately, the number of cases of *cavernous sinus thrombosis* is not great. It should be emphasized that an infection of the sinus may spread from a remote or localized infection and then produce the orbital congestion secondarily. The end result is usually the same but it is

difficult to determine the etiology at the onset. Lateral sinus thrombosis may also produce exophthalmos but this is by secondary edema. It is well to ascertain that this is not the true condition before the orbit is incised or explored. However, it is also well to know that the orbital lesion may be a pyocele or cellulitis before any attempt is made to drain a lateral or cavernous sinus.

Periostitis and osteitis are rather uncommon conditions of the orbit but I have seen cases in which there was a low grade, slowly progressive, painful type of exophthalmos. Although these diseases are usually thought to be due to lues the infections were nonspecific in my cases. Treatment is of little value but heat locally and deep therapy should be tried to afford relief of the pain.

Tenonitis as discussed under exophthalmos in children is similar in the adult except for one group of patients. In the serous or rheumatoid tenonitis associated with gout and general metabolic disorders, a greater number of cases of exophthalmos are recorded.

Fortunately, the protrusion is only 2 or 3 mm. The pain is out of proportion to the proptosis and is due to some involvement of the muscles. Rest, heat, and elimination of foci of infection are important. Heat by the cabinet or diathermy method may well be tried. Large doses of salicylates are beneficial and typhoid therapy is of value. The patient should have a specified dietary regimen.

The exophthalmos of *panophthalmitis* occurs late in the course of the disease and is slight but the pain again is out of proportion to and not due to the protrusion. The inflammatory process with the heavy cellular infiltration fills up the orbital space and the eye moves forward. In some instances, the entire globe is increased in size. Care is essential in handling these severe cases.

The method of handling *foreign bodies* in adults is the same as in children—those that are nonirritating are best left without treatment. The functional disturbance will probably not be as great as when one attempts too much surgical intervention.

An occasional case of infectious *granuloma* of the orbit has been reported, secondary inflammation being the cause of the exophthalmos. The infecting fungus may be actinomycosis, mycelium, or the blastomycosis. Draining sinuses from the orbit are produced and biopsy and careful bacteriological study are necessary to establish a diagnosis.

Hydatid or echinococcus cysts occur very uncommonly in the United States. The cyst is usually metastatic, the primary cyst being found in the liver.

Most *new growths* which produce exophthalmos are unilateral and noninflammatory. An increasing number of cases of inflammation of

the orbit are reported in which surgical intervention failed to reveal a tumor. Benedict drew attention to this some years ago and the name pseudotumor of the orbit has been given to this condition. In the presence of this inflammatory new growth, the eye and orbit are painful, the eye moves forward slowly, movement is limited and may be painful, and a gradual loss of vision takes place. Treatment by deep x-ray and local heat have been of little value. An associated infection of the sinus may be the etiological agent and careful study should be made in all cases. Exeneration may be required but the orbit continues to fill up with inflammatory tissue. True new growths of the orbit which produce inflammation and exophthalmos are rare although exophthalmos is the sign most common in all new growths. The displacement and the motility of the globe are important localizing signs. The progress of the protrusion, the associated pain, and its location should be taken into consideration.

Gummata are tertiary luetic manifestations which occur but rarely and they usually are unilateral. The positive blood test, the presence of scars from the primary lesion, or associated signs of lues should be looked for. The history and the onset of pain at night are aids in establishing the diagnosis. Trial therapeutic measures of neoarsphenamine or massive doses of potassium iodide may help to solve the problem and relieve the pain.

Tuberculoma are very rare and need only be mentioned as some cases are on record. They probably are the most difficult to diagnose preoperatively unless strong supporting evidence is present. As is true of tuberculosis in any part of the body, tuberculoma may break down and form a fistulous tract. Treatment should be directed toward general measures such as a high vitamin, high calorie diet, bed rest, and heliotherapy.

Exophthalmos from *carcinoma* is usually the result of metastasis or invasion. The glandular type arising from the lachrymal gland is fairly easy to diagnose and does not produce exophthalmos until late in the course of the disease. The eye is usually pushed downward and inward. Basal cell tumors of the lid should be treated early by radium or roentgenotherapy and then should be watched for recurrence or for new tumors in adjacent areas. Some of these tend to invade early and, although the invasion is inflammatory, it may be attributed to the previous radium or roentgenotherapy and the true nature overlooked. Here again exophthalmos is late and exeneration is necessary. Carcinoma which invade the orbit are quite common, usually coming from the antrum although the ethmoids and the sphenoids and rarely the frontal sinuses may be the seat of the original lesion.

These infiltrating carcinoma result in an early fixation of the globe with diplopia and a progressive type of exophthalmos. This is undoubtedly the most devastating of the new growths and requires radical methods of treatment. This condition is treated by radium or deep x-ray where possible. In other instances, radical exeneration and implantation of radium and use of x-ray are employed. It is advisable that patients who have had a malignancy of this type report at regular intervals over a period of time.

The *noninflammatory conditions* produce many cases of exophthalmos but are few in number.

The fracture of an orbital wall or loss of the wall due to syphilis or tuberculosis may result in the admittance of air into the tissues by way of the sinuses. Blowing the nose, sneezing, or coughing may push more air into the orbit and the exophthalmos may be sudden and serious. However, in most instances, pressure on the globe will usually meet with little resistance and a temporary pressure bandage may suffice to correct the condition. The patient must be warned about the cause of the condition and that care must be exercised or infection may be blown into the orbit by the same route.

Unilateral orbital edema due to *allergy* is rare but may occur. Unilateral edema due to congestion of the sinuses is seen. Shrinking of the nasal mucous membrane and irrigation of the sinus will aid in relieving the condition of the orbit and where drainage of a sinus is interfered with by a deviated septum or large boggy turbinate, the mechanical difficulty should be handled expeditiously. The instant there is involvement of the orbit, it is well to establish a diagnosis and institute treatment because any delay may mean a loss of vision.

Osteomata invading the orbit are not uncommon. They are produced by irritation of an associated sinus and may attain the size of a large robin's egg. Removal is necessary and the nose should be examined for any possible source of irritation. Many types of sarcoma invade the orbit and early removal is advisable. Most sarcomata in the orbit are not very inflammatory but form a fairly well isolated tumor mass which can be removed. The tumors arising from the orbital tissue do not, as a rule, metastasize early. Unless they are excised completely, they may recur. The method of approach is according to the location of the tumor. The lateral posterior route as advocated by Krönlein should not supersede other approaches unless one is relatively certain that the main tumor mass is well posterior and cannot be reached by easier and less traumatizing procedures.

Pulsating exophthalmos may be accompanied by visible pulsations which are also audible to the patient. It is fairly common and usually

unilateral. Certain features are common to both the traumatic and spontaneous types: (1) Both are acute; (2) the patient is conscious of the bruit; and (3) the exophthalmos is not great. Holloway reported a number of these cases and Locke, in 1924, collected a large series, giving an excellent description of the condition and the various forms of treatment. He found that the largest number of cases of pulsating exophthalmos were not spontaneous, but were due to trauma from injuries in automobile accidents. When this condition comes on, the patient is conscious that something has happened and there is an associated loss of vision which may produce complete blindness. Although there is some arterial circulation, the ischemia of the retinae is sufficient to cause loss of vision. The fall of arterial pressure results in a rise in the intra-ocular pressure and this also is probably a factor in disturbing the retinal circulation and producing a secondary anemia. Permanent changes in the retinal tissue may occur very soon because nervous elements do not tolerate lack of circulation over a very long period of time.

Locke described in detail the various types of treatment of pulsating exophthalmos by use of trial periods of compression. Gardner has employed muscle implants in the vessel, allowing them to drift to the site of rupture as advocated by Adson. This has met with considerable success. The condition, on the whole, is a serious one and the visual results, as a rule, are poor. Much of the exophthalmos remains because of the secondary fibrosis that takes place.

Intracranial aneurysms may cause exophthalmos because of remote congestion in the veins of the orbit. This is very unusual although Cushing and others have reported a number of cases. It is not easy to establish a diagnosis and the treatment must be directed by a neurosurgeon to the intracranial lesion.

A relative unilateral exophthalmos may occur in *thyroid disease.* We have not seen any cases in which the exophthalmos remained unilateral once the disease was established; however, cases have been reported by well qualified men and must be given consideration. It is safe to say, however, that given a case of unilateral exophthalmos with little substantiating evidence of thyroid disease, one should seek further for the cause and even in those cases where some thyroid disease is in evidence, other conditions should be carefully ruled out. The case in which widening of the palpebral fissures gives the appearance of exophthalmos is very misleading and, unless careful measurements are made, one is apt to make an incorrect diagnosis. Unequal exophthalmos is very misleading and, unless careful measurements are made, one is apt to make an incorrect diagnosis. It is also very common and because the measurements are of most value in each individual case

and because of the wide range of normals, it is well to keep in mind that protrusion on one side is a possibility. As mentioned previously, appearances are deceiving in the thyroid type of exophthalmos and great care should be taken in measuring and recording the progress of the protrusion.

Decrease in size of the orbit: The orbit reaches its adult size and shape fairly early in life, and although it expands slowly with normal growth of the individual, the relative proportions of the orbit to its contents remain the same. Therefore, any condition that diminishes the size of the bony vault pushes the contents out from the base of the cone and produces exophthalmos. Roentgen examination is very important in this group of cases because changes within the walls of the orbit can be visualized and comparative measurements can be worked out.

A common cause of decrease in the size of the orbit is trauma. Compression produces displacement of the orbit and a greater displacement of its contents. The eye may be very prominent for a time but slowly the orbital tissue atrophies and later there is a pronounced enophthalmos on the injured side. Other types of injury may bring the eye forward but, in most of these cases, atrophy and enophthalmos result. When the orbit and globe are displaced, a problem in the fitting of glasses arises which must be considered carefully. This is in the adjustment for the "off position eye." The patient may require a vertical prism and a decentration of the lens and a dropping of the frame on one side.

Changes in the bony vault are not very common causes of exophthalmos although we have seen cases of *hyperostosis* which involve the greater wing of the sphenoid and push the eye forward. Roentgen examination clearly defined the part of the vault which was involved, but no cause could be found, and the use of deep roentgenotherapy did not change the picture. Exostosis and sclerosing osteitis also may decrease the size of the orbit.

Endotheliomata of the vault of the skull sometimes produce an exostosis and displace the eye forward and downward.

Paget's disease may cause exophthalmos and loss of vision at the same time by involvement of the nerve in the canal. This condition is rarely seen, however, and is mentioned only as a possibility.

Bony growths *invading from the cranial vault* decrease the size of the vault and increase the content as well. Here again, roentgen examination will show the existing pathology in most instances.

Exophthalmos is a relatively common eye sign and it is always a sign of a disease process, either at the present time or at some past time. The diagnosis in many instances is not easy to make and the aid of

most of the other fields of medicine may be required. The notes presented here are mostly the result of my own observations and difficulties in diagnosing and treating this serious condition. The problem is to correct the primary cause and obtain a good cosmetic result with a functioning globe. The effort is worth the trial but most of the effort should be expended early—the earlier the diagnosis, the earlier the treatment which results in less protrusion, less residual change and the best functional result.

Patients with a protruding eye or eyes are never satisfied even though the primary condition is arrested or cured. If these notes prevent a single patient from the disfiguration and loss of vision due to exophthalmos, they have served their purpose.

THE FRANK E. BUNTS INSTITUTE

The Frank E. Bunts Institute announces the following course in "Diseases of the Gastro-Intestinal Tract," on Monday, Tuesday, and Wednesday, April 5, 6, and 7, 1937.

DISEASES OF THE GASTRO-INTESTINAL TRACT

Monday, April 5, 1937

8:30 A.M.	Registration.	
9:00 A.M.—9:45 A.M.	Dysphagia: Causes, Differential Diagnosis, and Roentgen Findings.	E. N. Collins, M. D.
9:45 A.M.—10:15 A.M.	Esophagoscopy: Treatment of Lesions in the Esophagus.	Paul M. Moore, M. D.
10:15 A.M.—10:45 A.M.	Surgical Treatment of Diverticula of the Esophagus.	T. E. Jones, M. D.
10:45 A.M.—11:15 A.M.	Dental Pathology as a Factor in Gastro-Intestinal Disease.	C. A. Resch, D. D. S.
11:15 A.M.—12:00 Noon	Diseases of the Stomach and Intestine Including Pancreatic Tumors, from a Surgical-Pathological Standpoint.	Allen Graham, M. D.
12:00 Noon—1:00 P.M.	Luncheon.	
1:00 P.M.—2:00 P.M.	Exhibits, Demonstrations.	
2:00 P.M.—2:30 P.M.	Etiology of Peptic Ulcer.	John Tucker, M. D.
2:30 P.M.—3:30 P.M.	Symptomatology, Diagnosis, and Medical Treatment of Diseases of the Stomach and Duodenum.	E. N. Collins, M. D.
3:30 P.M.—4:00 P.M.	Surgical Treatment of Diseases of the Stomach and Duodenum.	R. S. Dinsmore, M. D.
4:00 P.M.—5:00 P.M.	Nutritional Deficiency Disorders in Relation to Diseases of the Gastro-Intestinal Tract—Test Meals.	R. L. Haden, M. D.
6:00 P.M.	Dinner.	
8:15 P.M.	Frank E. Bunts Lecture: The Dysenteries.	T. T. Mackie, M. D. Research Associate, Department of Public Health and Preventative Medicine, Cornell University Medical College, New York City.

Tuesday, April 6, 1937

9:00 A.M.—9:30 A.M.	Gastro-Intestinal Symptoms Due to Cardiovascular Disease.	A. C. Ernstene, M. D.
9:30 A.M.—10:00 A.M.	Luetic Lesions of the Gastro-Intestinal Tract.	E. W. Netherton, M.D.
10:00 A.M.—10:45 A.M.	Differential Diagnosis of Jaundice.	C. L. Hartsock, M. D.
10:45 A.M.—11:15 A.M.	Liver Function Tests.	R. L. Haden, M. D.
11:15 A.M.—12:00 Noon	Pain in Right Upper Quadrant from the Roentgen Standpoint—Cholecystography.	B. H. Nichols, M. D.
12:00 Noon	Luncheon.	
1:00 P.M.—2:00 P.M.	Demonstrations. Exhibits. Practical Points in the Laboratory.	Alfred Reich, B. S.
2:00 P.M.—2:45 P.M.	Surgical Lesions of the Biliary Tract.	R. S. Dinsmore, M. D.
2:45 P.M.—3:45 P.M.	Fat Metabolism.	E. P. McCullagh, M.D.
3:45 P.M.—4:30 P.M.	Functional Disturbances of the Gastro-Intestinal Tract.	C. L. Hartsock, M. D.
4:30 P.M.—5:00 P.M.	Gastro-Intestinal Symptoms Due to Genito-Urinary Lesions.	W. E. Lower, M. D.
6:00 P.M.	Dinner. Round Table Discussion—Diagnostic Problems.	

Wednesday, April 7, 1937

9:00 A.M.—10:00 A.M.	Regional Enteritis. Ulcerative Lesions of the Colon.	E. N. COLLINS, M. D.
10:00 A.M.—10:30 A.M.	Management of the Patient with Pyloric and Intestinal Obstruction from Chemical Standpoint.	R. L. HADEN, M. D.
10:30 A.M.—11:15 A.M.	The Acute Abdomen, Including Surgical Complications.	R. S. DINSMORE, M. D.
11:15 A.M.—12:00 Noon	Allergy as a Factor in Gastro-Intestinal Disease.	I. M. HINNANT, M. D.
12:00 Noon	Luncheon.	
1:00 P.M.—2:00 P.M.	Exhibits.	
2:00 P.M.—2:30 P.M.	The Use of the Proctoscope in the Diagnosis of Diseases of the Anus and Rectum.	T. E. JONES, M. D.
2:30 P.M.—3:00 P.M.	The Roentgen Examination of the Colon.	J. C. ROOT, M. D.
3:00 P.M.—3:30 P.M.	Diagnosis and Treatment of Pruritis Ani and Vulvae.	E. W. NETHERTON, M.D.
3:30 P.M.—4:30 P.M.	Surgical Diseases of the Colon and Rectum.	T. E. JONES, M. D.

Thursday, April 8, 1937

SURGICAL CLINICS.

REGISTRATION BLANK

_____, 1937

THE FRANK E. BUNTS INSTITUTE
Cleveland Clinic
Cleveland, Ohio

Gentlemen:

Please register me for the course in "Diseases of the Gastro-Intestinal Tract," which is to be given April 5, 6, and 7, 1937.

I am enclosing a check for $5.00 and the remainder of the fee, $5.00, will be paid on registration, April 5.

Name_____

Address_____

_____

Medical School from which graduated.

NOTE: Checks should be made payable to The Frank E. Bunts Institute and sent to A. D. Ruedemann, M. D., Cleveland Clinic, Cleveland, Ohio.

Exhibits

Roentgen Findings in Diseases of the Gastro-Intestinal Tract ..... Dr. E. N. Collins and Dr. J. C. Root

Nutritional Deficiency Disease ..... Dr. R. L. Haden

Dietary Treatment of Urinary Calculi ..... Dr. C. C. Higgins and Dr. F. C. Schlumberger

Allergy ..... Dr. I. M. Hinnant

Carcinoma of the Rectum and Colon ..... Dr. T. E. Jones

Charts Demonstrating the Biochemistry and Physiology of Digestion ..... Dr. D. Roy McCullagh

Protamine-Zinc-Insulin in Diabetes ..... Dr. E. Perry McCullagh

Use of Pitressin as an Aid in Cholecystography ..... Dr. J. C. Root and Dr. E. N. Collins

Pathological Specimens ..... Dr. Allen Graham

Dental Roentgenograms ..... Dr. C. A. Resch

Wax Models of Lesions of the Gastro-Intestinal Tract.

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The Museum of Comparative Anatomy of the Energy-Controlling Mechanism will be open.